The Journal of Pediatrics

VOL. 12 MAY, 1938 NO. 5

Original Communications

FOCAL INFECTION AND METABOLISM

THE EFFECT OF THE REMOVAL OF TONSILS AND ADENOIDS ON THE NITROGEN BALANCE AND THE BASAL METABOLISM

J. A. JOHNSTON AND J. W. MARONEY, M.D.
DETROIT, MICH.

CLINICAL evidence of improved nutrition, as judged by weight gain, has been repeatedly observed following tonsillectomy.[1, 2] Kaiser,[3] however, although finding a reduction in the incidence of malnutrition nine to twelve months following the operation, points out that since 66 per cent of his group were normal before the procedure, diseased tonsils are not necessarily associated with malnutrition. That the weight is an inadequate measure of nutrition, we have previously pointed out;[4] it may be maintained over considerable periods during which nitrogen is being lost from the body and the basal metabolism is falling. We are constantly impressed, however, with the observation that malnutrition in the middle economic stratum is, in a majority of instances, the result, not of poor feeding, but of disease. In a group of 100 cases in this clinic in which the diagnosis of malnutrition was made following a complete physical examination, an adequate diet seemed to be available for all but three patients; definite organic disease was evident in 86, and, of these, 65 had infections of the upper respiratory tract—tonsils, adenoids, and sinuses. In the lower economic stratum, these figures would undoubtedly not hold, and the availability of food would play a more prominent rôle.

THE LITERATURE

The effect of infection on a number of phases of metabolism has been studied. Studies on the total metabolism are to a large extent complicated by the presence of fever; when this is true, the height of the total metabolism parallels the fever.[5]

The most striking effect is that observed on the nitrogen balance, a marked diminution occurring, and while this may be prevented, it

From the Department of Pediatrics and the Department of Laboratories, Henry Ford Hospital.

requires an addition to the diet of a number of calories greater than the increment incidental to the febrile process. Coleman and Du Bois[6] say: "It is impossible to escape the conclusion that the destruction of protein is caused by the toxins of the disease." In a critical discussion of the point, Peters and Van Slyke[7] make this comment: "Protein destruction parallels the intensity of intoxication rather than the temperature . . . 'toxic destruction' is not merely an expression, as in hyperthyroidism, of greater energy requirement. It is rather due to autolysis of tissue."

While this communication limits itself to a consideration of the total and the protein metabolism, some consideration of carbohydrate metabolism is inevitable, so interdependent are nitrogen and sugar. Numerous studies on the effect of infection on carbohydrate metabolism show an impairment as judged by the tolerance curve.[8] Pemberton and Foster,[9] however, whose curves before and after the removal of infected tonsils and teeth are most striking, say this: "It is to be doubted whether the disturbance . . . is confined to carbohydrate alone. There are reasons for believing it to be the expression of a widespread function in which the fats and possibly in some degree the nitrogenous elements may be involved." Much of this and similar work possibly should be reinterpreted in the light of Johnston's studies[10] which showed that the amount of glucose oxidized at any given time bore a straight-line relation to the amount available in the body at that time. One of his subjects was a chronic arthritic like those studied by Pemberton and Foster, and, while initially he showed the depression of oxidation incidental to depleted stores, a normal utilization could be demonstrated merely by restoring the glycogen reserves by the injection of intravenous glucose. Richardson and Levine[11] feel that the ill effects of infection in diabetes are due, not to any disturbance in the ketogenic balance, as suggested by Wilder and Winter,[12] but to an actual reduction in the amount or proportion of glucose oxidized. The inference from all of this work is that there is no specific effect on carbohydrate metabolism in infection but merely that incidental to depletion as a result of increased metabolic need.

The attempt to interpret the effect of chronic infection on the basal metabolism must take into account the fact that this will be the resultant of two opposing forces; the elevation attendant on infection will be offset to a large extent by the depression incidental to malnutrition. McCann[13] felt this accounted for the comparatively normal rates which he found in tuberculosis. It should be noted, however, that all of his subjects were definitely undernourished.

In substance, infection is known definitely to elevate the total metabolism, though how much of this can be attributed to the rise in temperature and how much to the toxic process is not clear. It is well

established that the effect on nitrogen metabolism is of a magnitude too great to be explained as a mere function of the total metabolic change. The impairment of carbohydrate metabolism is almost certainly nonspecific and understandable as the result of depleted reserves.

PLAN AND METHODS

The subjects were nine children varying in age from 5 to 13 years, selected from the current admissions for tonsillectomy solely on the basis of the feasibility of their remaining in the hospital for the study

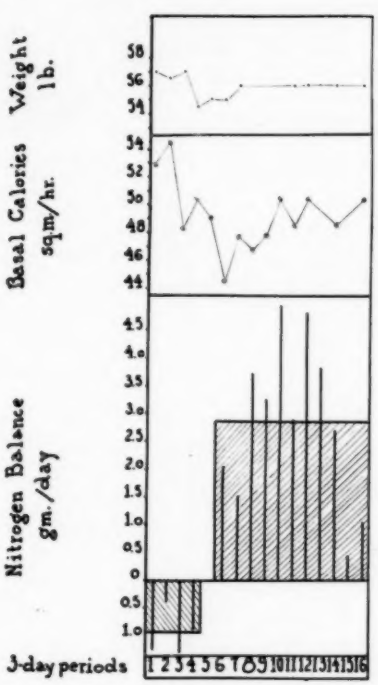

Fig. 1.

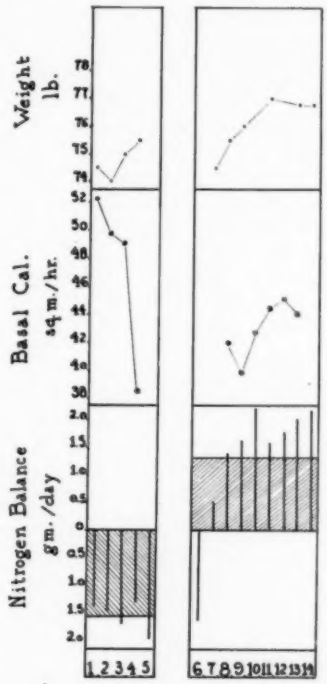

Fig. 2.

Fig. 1.—F. S., male 9 years old. Height, 50 inches. Estimated weight, 58 pounds. Tonsillectomy first day, fifth period.
Nitrogen balance and basal metabolism before and after removal of tonsils and adenoids. In this and subsequent charts the balances are continuous; each bar represents a three-day balance, and the average of all balances before and after is indicated by crosshatching.

Fig. 2.—S. R., male 13 years old. Height, 56 inches. Estimated weight, 78 pounds. Tonsillectomy first day, sixth period.
Nitrogen balance and basal metabolism before and after removal of tonsils and adenoids. The balances are continuous and the diet constant. Each bar represents a three-day balance, and the average of all periods before and after tonsillectomy is shown by crosshatching.

period. All of the children gave histories of recurrent throat infections and all showed enlargement and scarring of the tonsils and some enlargement of the cervical lymph nodes; none showed clinical evidence

of recent infection at the time of admission. In weight there was an average departure from the Baldwin-Wood standards of –6 per cent. During the period of study prior to operation, the children carried on a schedule of activity including attendance at school in the hospital. This schedule was resumed within a week after operation in each instance.

The diets used were calculated from the revised food standards of Atwater and Bryant[14] and Waller[15] and were weighed in the hospital diet kitchen. The caloric intakes were designed on the basis of

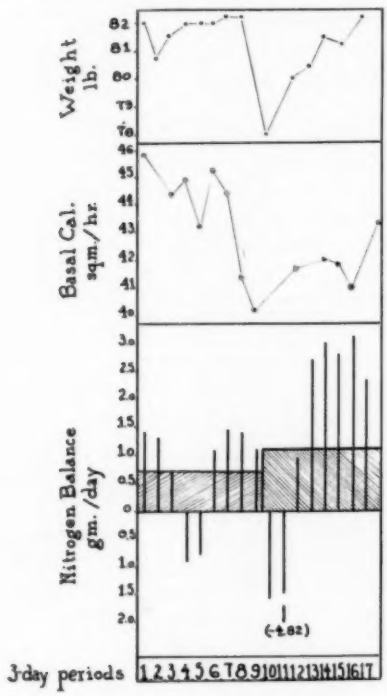

Fig. 3.—J. L., male 13 years old. Height, 58 inches. Estimated weight, 85 pounds. Tonsillectomy second day, tenth period.
Nitrogen balance and basal metabolism before and after removal of tonsils and adenoids. The balances are continuous. Each bar represents a three-day balance. The average of all balances before and after the tonsillectomy is indicated by crosshatching.

previous studies[4] to maintain a positive nitrogen balance and a level or positive weight curve, and were apportioned 15 per cent to protein, 35 per cent to fat and 50 per cent to carbohydrate. In the four earlier and shorter studies a varied diet was used. In the five children studied for longer periods, six fixed diets of the same caloric and percentage composition were used in six-day rotation. Analysis of these diets by digestion in sulfuric acid and analysis for nitrogen by the Kjeldahl-

Gunning procedure for thirty-eight consecutive six-day periods has shown a mean deviation from the estimated nitrogen content of +3 per cent. For the first three days following operation a liquid diet was used and the nitrogen content estimated from the tables.

Determinations of the urine nitrogen were made daily and of the stool nitrogen in three-day periods by the Kjeldahl-Gunning procedure. Determinations of basal metabolism were planned to correlate with each three-day nitrogen balance; gas collections were made with the Tissot tank and analyses with the Haldane-Henderson apparatus.

Tonsillectomies were performed by dissection and snare under nitrous oxide and ether anesthesia. Adenoidectomies were also done. Microscopic sections were prepared in each case. None showed evidence of tuberculosis, but all showed chronic inflammation. In one patient (J. L., Case 9) there was found a frank abscess at the base of one tonsil.

FINDINGS

These are recorded in detail on three subjects (Tables I, II, and III, and Figs. 1-3) and Table IV summarizes the data for all nine cases. With a single exception (Case 8) the findings are very consistent,

TABLE I

F. S. Height 50 inches
Birth date, 1929. Weight 57 lb.
Admitted Dec. 15, 1936, for tonsillectomy (chr. inf.) Est. weight 58 lb.
Dec. 29, 1936.

Standard Experimental Diet 1-6; 1400 Cals. 15-35-50%; P. 52.5 gm., F. 70.0 gm., C. 175 gm.

PERIOD	DATE, 1936-1937	NITROGEN					B.M.R.	R.Q.	CAL./SQ. M./HR.	TOTAL CAL.	HEIGHT	WEIGHT
		AVERAGE URINE	AVERAGE STOOL	OUTPUT	INTAKE	BALANCE						
1	12/18-20	9.94	1.28	11.22	9.95	-1.27						
2	12/21-23	9.42	0.86	10.28	9.95	-0.33	+ 4	0.81	52.9	1226	50	57
3	12/24-26	9.93	1.35	11.28	9.95	-1.32	+ 7	0.82	54.4	1253		56½
4	12/27-29	9.56	1.26	10.82	9.95	-0.87	- 4	0.82	48.2	1112		57
	12/30-1/1				*Mean Balance -0.95*							
5	1/ 2- 4	7.31	0.78	8.09	9.37	+2.06	± 0	0.81	50.4	1135		54½
6	1/ 5- 7	7.22	0.97	8.19	8.74	+1.52	- 2	0.80	49.0	1141		55
7	1/ 8-10	6.25	0.63	6.88	9.95	+3.70	-11	0.88	44.5	1015		55
8	1/11-13	5.72	1.00	6.72	9.95	+3.23	- 6	0.84	47.6	1097		56
9	1/14-16	4.26	0.75	5.01	9.95	+4.94	- 7	0.84	36.7	1073		56
10	1/17-19	5.65	1.47	7.12	9.95	+2.83	- 5	0.82	47.7	1100		56
11	1/20-22	4.13	0.93	5.06	9.95	+4.89	+ 0	0.81	50.4	1159		56
12	1/24-25	5.70	0.46	6.16	9.95	+3.79						
13	1/26-28	6.35	0.99	7.34	9.95	+2.61	- 3	0.79	48.5	1118		56
14	1/29-31	8.75	0.74	9.49	9.95	+0.46						
15	2/ 1- 3	8.36	0.56	8.92	9.95	+1.03	± 0	0.81	50.4	1160		56
					Mean Balance +2.82							

showing a striking improvement in the utilization of nitrogen with the removal of the focus of infection. This is out of all proportion to any increase that might be related to a replenishment of stores lost incidental to anesthesia and food withdrawal on the day of operation and several days of convalescence. In several instances, collections of urine and stool, and accurate measurements of intake proceeded uninterruptedly throughout this period in order to make this estimation possible; in others, a considerable period was allowed to elapse following the operation, to move the determination further from this influence.

TABLE II

S. R. Height 56 inches
Birth date, March 6, 1924. Weight 74½ lb.
Admitted July 2, 1937, for tonsillectomy (chr. inf.) Aug. 5, 1937. Est. weight 78 lb.
Standard Experimental Diet 1-6; 2200 Cal. 15-35-50%; P. 82.5 gm., F. 85.5 gm., C. 275 gm.

		NITROGEN										
PERIOD	DATE, 1937	AVERAGE URINE	AVERAGE STOOL	OUTPUT	INTAKE	BALANCE	B.M.R.	R.Q.	CAL./SQ. M./HR.	TOTAL CAL.	HEIGHT	WEIGHT
1	7/ 4- 6	14.03	0.56	14.59	13.27	−1.32	+13	0.96	52.3	1469	56	74½
2	7/ 7- 9	13.83	0.81	14.64	13.17	−1.47	+ 8	0.78	49.9	1390	56	74
3	7/10-12	14.13	0.79	14.92	13.27	−1.65	+ 6	0.74	49.1	1378	56	75
4	7/13-15	13.80	0.74	14.54	13.20	−1.34	−16	0.80	38.6	1082	56	75½
5	7/16-18	14.53	0.67	15.20	13.27	−1.93						
		Control Period—Mean Balance −1.54										
	8/ 5	T & A										
6	8/ 6- 8	9.61	0.83	10.44	8.84	−1.60	− 5	0.81	43.6	1224	56	74¼
7	8/ 9-11	8.74	0.39	9.13	9.63	+0.50						
8	8/12-14	10.16	0.84	11.00	12.37	+1.37	− 9	0.78	42.0	1178	56	74½
9	8/15-17	10.84	0.85	11.69	13.27	+1.58	−13	0.73	39.9	1128	56	75½
10	8/18-20	9.89	1.00	10.89	13.27	+2.38	− 7	0.72	42.8	1212	56½	76
11	8/21-23	10.95	0.79	11.74	13.27	+1.53						
12	8/24-26	10.95	0.58	11.53	13.27	+1.74	− 3	0.81	44.5	1260	56½	77
13	8/27-29	10.61	0.67	11.28	13.27	+1.99	− 2	0.76	45.3	1282	56½	76¾
14	8/20-9/1	10.13	1.02	11.15	13.27	+2.12	− 5	0.78	44.1	1270	56½	76¼
		Mean Balance +1.29										

The basal metabolism figures show a definite fall following tonsillectomy. Part of this may be attributable to the bed rest of convalescence and the nitrogen loss incidental to the operation, and it is true that the lowest figures are obtained just after the procedure, but even when activity has been restored and nitrogen is being conserved, the level of basal readings is much lower than preoperatively.

If the determinations in the period following tonsillectomy are considered separately, there is a suggestion of the curious phenomenon of a rough direct parallelism between nitrogen retained and the basal rate; a rising rate seems to parallel a rising retention. This is, of

TABLE III

J. L. Height 58 inches
Birth date, Nov. 2, 1924 Weight 82 lb.
Admitted Sept. 23, 1937, for tonsillectomy (chr. inf.) Oct. 21, 1937. Estimated wt. 85 lb.
Standard Experimental Diet 1-6; 2000 Cal. 15-35-50%; P. 82.5 gm.; F. 85.5 gm.; C. 275 gm.

		NITROGEN										
PERIOD	DATE, 1937	AVERAGE URINE	AVERAGE STOOL	OUTPUT	INTAKE	BALANCE	B.M.R.	R.Q.	CAL./SQ. M./HR.	TOTAL CAL.	HEIGHT	WEIGHT
1	9/25-26	10.40	1.34	11.74	13.20	+1.46	- 1	0.86	45.9	1365	58	82
2	9/27-29	9.63	2.21	11.84	13.20	+1.36						
3	9/30-10/2	11.46	1.10	12.56	13.20	+0.64	- 5	0.83	44.3	1318		80¾
4	10/ 3- 5	12.43	1.37	13.80	12.86	-0.94	- 3	0.86	44.9	1347		81½
5	10/ 6- 8	12.70	1.29	13.99	13.20	-0.79	- 6	0.85	43.2	1296		82
6	10/ 9-11	11.00	1.17	12.17	13.20	+1.03	- 2	0.83	45.2	1356		82
7	10/12-14	10.50	1.23	11.73	13.20	+1.47	- 4	0.79	44.4	1278		82
8	10/15-17	10.14	1.60	11.74	13.20	+1.46						
9	10/18-20	10.87	1.25	12.12	13.20	+1.08	-10	0.80	41.3	1248		82½
		Control Period—Mean Balance +0.75										
	10/22	*Tonsillectomy**										
10	10/21-23	9.34		9.34	7.68	-1.66	-13	0.84	40.2	1206		82
11	10/24-26	9.64	1.09	10.73	5.91	-4.82						
12	10/27-29	10.87	1.15	12.02	13.10	+0.98	-10	0.83	41.7	1220		78
13	10/30-11/1	9.63	0.78	10.41	13.10	+2.69	- 9	0.84	42.0	1249		80
14	11/ 2- 4	8.63	1.46	10.09	13.10	+3.01	-10	0.84	41.8	1243		80½
15	11/ 5- 7	8.93	1.29	10.22	13.10	+2.88						
16	11/ 8-10	9.21	0.82	10.03	13.10	+3.07	-12	0.78	40.7	1226		81¼
17	11/11-13	9.41	1.56	10.97	13.10	+2.13	-12	0.79	40.9	1226		81
18	11/14-16	9.17	0.63	9.80	13.20	+3.40	- 6	0.84	43.6	1308		82
		Posttonsillectomy—Mean Balance +1.30										

*Abscess found at base of tonsil at operation.

TABLE IV

SUMMARY METABOLIC OBSERVATIONS BEFORE AND AFTER TONSILLECTOMY

					NITROGEN BALANCE				BASAL METABOLISM			
					BEFORE		AFTER		BEFORE		AFTER	
SUBJECT	SEX	AGE	WEIGHT*	EST. WEIGHT	NO. DAYS	AV./DAY	NO. DAYS	AV./DAY	CAL./SQ. M./HR.	R.Q.	CAL./SQ. M./HR.	R.Q.
1. F. S.	M	9	56	58	12	-0.95	33	+2.82	51.8	0.82	48.3	0.83
2. J. C.	M	11	68½	71	7	-1.16	5	+3.62	51.7	0.79	57.7	0.77
3. J. L.	M	12	81	90	3	+0.05	6	+1.35	51.6	0.82	47.0	0.82
4. P. A.	M	5	45	56	11	-0.40	6	+0.18	54.0	0.95	55.0	0.95
5. A. C.	F	9	56	53	3	+2.27	3	+3.45	45.7	0.80	43.6	0.82
6. S. R.	M	13	74½	78	15	-1.54	27	+1.29	47.5	0.82	43.1	0.76
7. J. D.	M	8	45	53	17	+0.21	24	+0.34†	49.8	0.81	46.3	0.85
8. F. R.	M	10	63	67	15	+1.62	21	+1.33†	45.6	0.88	43.9	0.85
9. J. L.	M	13	82	85	26	+0.72	24	+1.04†	43.7	0.84	41.8	0.83
Average						+0.06‡		+1.52	49.0	0.83	46.7	0.83

*Average deviation from Baldwin-Wood tables equals 6 per cent.
†Includes loss incidental to operative procedure and refusal of food thereafter.
‡Individual balance averages weighted according to number of days' observation.

course, directly opposed to our concept of the relation between these two items, though a similar finding obtains in pregnancy and has been thought of as the result of a new protoplasmic mass. Whether this can be dismissed as a function of the growth period, or whether or not the influence of another hormone (growth ?) must be invoked to explain it, we do not know. We have made a similar observation in mild hyperthyroidism and in the cretin to whom thyroid was being administered, i.e., a rising metabolic rate paralleling synthesis of tissue, as judged by increased nitrogen storage, rather than catabolism with increased nitrogen loss, the usual finding in the adult.

The point is worthy of some note in the light it may throw on the action of a focal infection on the growth process.

SUMMARY

The removal of infected tonsils was followed by a fall in basal metabolism and an increase in nitrogen retention.

The improvement in nitrogen utilization would seem to be out of proportion to anything that might be accounted for as a result of a fall in basal metabolism incidental to the removal of the infection.

Dr. F. W. Hartman supervised the metabolism determinations and reviewed the sections of the removed tonsils; Dr. O. H. Gaebler supervised the determinations of nitrogen balance.

REFERENCES

1. Paterson, D., and Bray, G. W.: Lancet **2**: 1074, 1928.
2. Keen, J. A.: Lancet **1**: 979, 1933.
3. Kaiser, A. D.: Am. J. Dis. Child. **23**: 139, 1922.
4. Maroney, J. W., and Johnston, J. A.: Am. J. Dis. Child. **54**: 29, 1937.
5. Du Bois, E. F.: Basal Metabolism in Health and Disease, ed. 2, Philadelphia, 1927, Lea & Febiger, p. 391.
6. Coleman, W., and Du Bois, E. F.: Arch. Int. Med. **15**: 885, 1915.
7. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Vol. 1, Interpretations, 1931, Williams & Wilkins, p. 295.
8. Olmstead, W. H., and Gay, L. P.: Arch. Int. Med. **29**: 384, 1922.
9. Pemberton, R., and Foster, G. L.: Arch. Int. Med. **25**: 243, 1920.
10. Johnston, J. A.: Am. J. Dis. Child. **46**: 309, 1933.
11. Richardson, H. B., and Levine, S. Z.: J. Biol. Chem. **63**: 465, 1925.
12. Wilder, R. M., and Winter, M. D.: J. Biol. Chem. **52**: 393, 1922.
13. McCann, W. S.: Arch. Int. Med. **29**: 33, 1922.
14. Atwater, W. O., and Bryant, A. P.: Bulletin 28, United States Department of Agriculture.
15. Waller, D. S.: Nutritive Value of Food, Ann Arbor, 1932, George Wahr.

IMMUNOLOGIC REACTIONS FOR UNDULANT FEVER IN APPARENTLY HEALTHY AND IN TUBERCULOUS CHILDREN

JULIAN R. LEWIN AND ISADORE GERSH, M.D.
DENVER, COLO.

DURING a recent study of the incidence of undulant fever in Colorado by Gersh and Mugrage[1] several problems presented themselves which were considered worthy of further investigation. Among these were (1) the incidence of immunologic reactions for undulant fever in children; (2) the comparative occurrence of positive reactions for undulant fever in apparently healthy children and in those confined in an institution for the tuberculous; and (3) the relation of the ingestion of raw milk to the incidence of positive immunologic reactions.

It is recognized that in spite of the fact that milk constitutes a larger factor in the diet of children than in adults, the incidence of clinical undulant fever in the former is less.[2] Larson and Sedgwick[3] examined the blood of 425 children by the complement fixation and agglutination methods and found an incidence of 17 per cent positive reactions. The results of these two tests paralleled each other, but the results of other workers are not in accord. In a personal communication to Wolter,[4] Madsen states that in a large children's hospital in Copenhagen, a region where a great deal of raw milk is consumed and Brucella infection is prevalent, he found no positive agglutination reactions in children under 10 years of age. Guest[5] applied abortus agglutination tests to 250 serums obtained at Children's Hospital, Boston, and found only one positive reaction through a titer of 1:40. Dietrich and Bonynge[6] performed agglutination tests on the serums of 1,000 children from infancy to 10 years of age and found only one positive reaction. They suggest that the low incidence in childhood is due to (1) lack of contact with infected animals; (2) low pathogenicity of the bovine variety of *Brucella melitensis* for man, especially when ingested; (3) generally small numbers of organisms ingested; and (4) biologic immaturity of the tissues of the infant and young child.

In our study a total of 310 children were examined. In the first group of 222 children, 170 were apparently healthy,* while 52† were in an institution for the tuberculous, either because of active disease, or malnutrition associated with definite or probable exposure to infec-

From the Department of Clinical Pathology, University of Colorado School of Medicine.
*From the Colorado State Home for Dependent Children, Denver.
†From the National Jewish Hospital, Denver.

TABLE I

INCIDENCE OF IMMUNOLOGIC REACTIONS FOR UNDULANT FEVER

STATUS OF CHILDREN	TOTAL NO.	NUMBER OF POSITIVE AGGLUTINATION TESTS	PERCENTAGE OF POSITIVE AGGLUTINATION TESTS	NUMBER OF POSITIVE SKIN REACTIONS	PERCENTAGE OF POSITIVE SKIN REACTIONS	NUMBER GIVING POSITIVE HISTORY OF RAW MILK INGESTION	PERCENTAGE GIVING HISTORY OF RAW MILK INGESTION
Apparently Healthy	170	0	0	6	3.5	81	47.6
Actively Tuberculous*	17	0	0	3	17.7	12	70.6
Inmates of Preventorium*	35	1	2.8	3	8.6	14	40.0
Total	222	1	0.45	12	5.4	107	48.2

*National Jewish Hospital.

tion. The second group of 88 were patients under observation in the outpatient department of the Colorado General Hospital.

The first group of 222 children, whose ages ranged from 4 to 16 years, were examined for evidence of immunologic responses to undulant fever by means of agglutination and skin tests. For the agglutination test three dilutions of blood serum (1:20, 1:50, and 1:100) were examined by the technique outlined by Gersh and Mugrage.[1] The skin test was done by injecting intradermally into the anterior aspect of the forearm 0.1 c.c. of a suspension of *Brucella melitensis* organisms (containing 600 million killed bacteria per cubic centimeter). The local reactions were read forty-eight hours later and interpreted on the basis of the area of swelling, induration and erythema and were graded according to the method described by Gersh and Mugrage.[1] The results of these tests are given in Table I.

The blood showing the positive agglutination reaction was from a 12-year-old boy in the preventorium who had lived on a farm in Texas for four months during the year of 1936. Agglutinins were found in dilutions of 1:20, 1:50, and 1:100. A study of Table I reveals, first, that the incidence of intradermal immunologic reactions for undulant fever in the series of apparently healthy children is 3.53 per cent, considerably less than that encountered in adults by Gersh and Mugrage;[1] second, that the occurrence of positive reactions for undulant fever in those children confined in the preventorium is greater than that in apparently healthy children; and, third, that the incidence is greater in those children with active tuberculosis than in children confined in the preventorium.

Inasmuch as raw milk is generally recognized as a common source of infection in undulant fever, it was interesting to note that all those showing positive intradermal reactions gave a history of the ingestion of raw milk. However, it must be noted that of the 222 children, 107 (48.2 per cent) gave definite histories of raw milk ingestion and yet showed no immunologic responses for undulant fever. This would suggest that the susceptibility of the individual and perhaps the size and frequency of the dosage of organisms play a major rôle in infection.

An attempt was made to determine the frequency with which undulant fever and tuberculosis are associated in children. For this study tuberculin tests by the Mantoux method and skin tests for sensitization to *Brucella melitensis* were performed simultaneously on the second group of 88 children from the ages of 7 months to 15 years, entering the outpatient department of the Colorado General Hospital. In addition, there was incorporated in this study the results obtained at the National Jewish Hospital, also a review of the clinical records of these patients. The results of these investigations are given in Table II.

TABLE II

COMPARATIVE INCIDENCE OF INTRADERMAL IMMUNOLOGIC REACTIONS FOR UNDULANT FEVER AND TUBERCULOSIS

	TOTAL NUMBER	NO. GIVING HISTORIES OF INGESTION OF RAW MILK	% GIVING HISTORIES OF INGESTION OF RAW MILK	NO. GIVING POSITIVE TUBERCULIN REACTION	% GIVING POSITIVE TUBERCULIN REACTION	NO. GIVING POSITIVE SKIN REACTION TO BR. MELITENSIS	% GIVING POSITIVE SKIN REACTION TO BR. MELITENSIS	NO. GIVING POSITIVE SKIN REACTION, ALSO POSITIVE TUBERCULIN REACTION	% GIVING POSITIVE SKIN REACTION, ALSO POSITIVE TUBERCULIN REACTION
From outpatient department of the Colorado General Hospital	88	36	40.9	19	21.6	4	4.5	2	50.0
From the National Jewish Hospital	52	26	50.0	31	59.6	6	11.5	5	83.3

The results of these studies both on apparently healthy children and those confined in an institution for the tuberculous would suggest either that raw milk serves as a common source of infection for undulant fever as well as for tuberculosis, or that tuberculosis renders the individual less resistant to infection by *Brucella melitensis.*

CONCLUSIONS

1. The incidence of immunologic reactions for undulant fever in children is considerably less than that encountered in adults.

2. The frequency of positive immunologic reactions for undulant fever in children with either tuberculous infection or history of exposure to tuberculosis seems to be greater than that in apparently healthy children.

3. The commonly reported parallelism between the ingestion of raw milk and the frequency of positive immunologic responses to undulant fever receives additional support from this study.

The authors wish to acknowledge the courtesy of Dr. William Wiley Jones and Dr. Charles J. Kaufman, for permission to study groups of children under their care, and to thank Dr. D. J. Musman for his assistance in the performance of the tests.

REFERENCES

1. Gersh, I., and Mugrage, E. R.: J. Lab. & Clin. Med., To be published.
2. Hardy, A. V.: J. A. M. A. **93**: 891, 1929.
3. Larson, W. P., and Sedgwick, J. P.: Am. J. Dis. Child. **6**: 326, 1913.
4. Wolter, Fried.: Wurzburger Abhandlungen aus dem Gesamtgebiet der Medizin **27**: Part V, 1931.
5. Guest, G. M.: Ohio State M. J. **26**: 221, 1930.
6. Dietrich, H., and Bonynge, C. W.: J. PEDIAT. **1**: 46, 1932.

THE EFFECTS OF TANNIC ACID NASAL SPRAYS ON THE INCIDENCE OF UPPER RESPIRATORY INFECTIONS

MARGARET HARPER MCKEE, M.D.
IRVINGTON, N. Y.

IN VIEW of the fact that many rheumatic recurrences are closely associated with upper respiratory infections, the importance of reducing the incidence of these infections in an institution for convalescent rheumatic children is obvious. It is now generally accepted that the common cold is due to a filtrable virus which prepares the way for secondary bacterial invasion.[1] It has been shown by Olitsky and his co-workers that local treatment of the nasal passages of animals prevents infection with certain neurotropic viruses.[2-4] Although there is no evidence that the virus of the common cold has an affinity for the nervous system, it was thought of interest to see if the incidence of the common cold could be reduced by blocking the nasal passages.

Nasal sprays containing various chemicals such as tannic acid, picric acid, sodium alum, and zinc sulfate have been used successfully in animals by different workers to prevent infection with filtrable viruses.[5-7] In man there have been occasional reports of toxic effects following the use of picric acid intranasally.[8]

In this study to determine the effect of blocking the nasal passages on the incidence of the common cold, tannic acid was chosen as the most suitable reagent because of its lack of toxicity. Since 3 per cent solutions of tannic acid had been found to be only partially effective in the protection of monkeys against poliomyelitis, it was decided to use a 4 per cent solution in this investigation.[3]

PROCEDURE

One hundred and five children with rheumatic heart disease were available for this study. Most of the patients were admitted before November, 1936, and with a few exceptions, remained throughout the winter months. The majority of the patients were ambulatory. They attended school in the same building and had no contact with children outside of the institution. The number of visitors for each child was limited to two adults every six weeks. (This institution is situated in the country, 22 miles from New York City.)

The 105 children were divided into two groups, using alternate cases from an alphabetical list. Fifty-four were sprayed, and 51 received no treatment and constituted the controls.

From Irvington House. This work was aided by a grant from the Commonwealth Fund.

METHODS

Four per cent chemically pure tannic acid was dissolved in distilled water and sterilized by autoclaving to prevent contamination with molds. This solution was administered by ordinary nasal spray daily for one week beginning Nov. 16, 1936, and then once a week thereafter until April 1, 1937.

The two groups were observed for the occurrence of upper respiratory infections. Routine cultures for the isolation of hemolytic streptococci were made at frequent intervals to determine the carrier rate. Throat cultures were also made on all children at the time that they had colds to determine the incidence of hemolytic streptococci.

Tannic acid in the concentration used produces a mildly uncomfortable prickly astringent feeling of the nose and throat for five or ten minutes, followed by a mucoid discharge varying in intensity with the individual, lasting from twenty minutes to one hour. These effects are somewhat less pronounced after repeated treatments. None of the children objected seriously to the treatments although most of them considered them unpleasant.

RESULTS

Approximately 70 per cent of the children in each group had one or more upper respiratory infections during the period of observation, November, 1936, to April, 1937, averaging 1.1 or 1.2 episodes per patient. In about 50 per cent of the cases the predominating symptoms and signs were localized in the throat, and in the rest the nasal passages were mainly involved. The number of children having obvious chronic sinusitis was about evenly divided. Four untreated and only one treated child had frank tonsillitis associated with a marked elevation of temperature, but the total number of this type of infection is too small to draw conclusions. The number of upper respiratory

TABLE I

	TREATED (54)	CONTROL (51)	TOTAL (105)
Upper respiratory infection, patients	37	36	73
Upper respiratory infection, bed days	213	233	448
Upper respiratory infection, episodes	61	63	124
Pharyngitis	28	33	61
Tonsillitis	1	4	5
Coryza	32	25	57
Chronic sinusitis	7	5	12
Adenitis	-	1	1
Upper respiratory infection and streptococcus	11	12	23
Rheumatic recurrences	9	11	20
Preceded by upper respiratory infection and *Streptococcus hemolyticus*	2	5	7
Upper respiratory infection without *Streptococcus hemolyticus*	1	3	4
No antecedent upper respiratory infection	6	3	9
Streptococcus carriers	8	10	18

infections associated with streptococci was almost identical, and the number of streptococcus carriers was approximately the same in the treated and the control groups. The number of attacks of rheumatic fever in the two groups was nearly alike: three attacks in the treated and eight in the untreated children were preceded by upper respiratory infections; and of these, two in the treated and five in the control group were associated with streptococci.

The findings are summarized in Table I.

DISCUSSION

No significant difference was observed between the treated group and the untreated group. It is probable that blocking of the nasal passages affords effective protection only in those diseases which are caused by strictly neurotropic viruses.

CONCLUSIONS

Nasal sprays of tannic acid administered as described above, failed to reduce: the incidence of upper respiratory infections; the incidence of upper respiratory infections associated with streptococci; and the incidence of rheumatic recurrences.

REFERENCES

1. Dochez, A., and Hanger, F. McC., Jr.: Oxford Medicine, Vol. 4, p. 939.
2. Olitsky, P. K., and Cox, H. R.: Science **80**: 566, 1934.
3. Sabin, A. B., Olitsky, P. K., and Cox, H. R.: J. Exper. Med. **63**: 877, 1936.
4. Olitsky, P. K., and Sabin, A. B.: Proc. Soc. for Exper. Biol. & Med. **36**: 532, 1937.
5. Armstrong, C.: Pub. Health Rep. **50**: 43, 1935.
6. Armstrong, C., and Harrison, W. T.: Pub. Health Rep. **50**: 725, 1935.
7. Schultz, E. W., and Gebhardt, L. P.: Proc. Soc. Exper. Biol. & Med. **35**: 525, 1937.
8. Queries and Minor Notes, J. A. M. A. **107**: 1322, 1937.

HURLER'S SYNDROME (GARGOYLISM)

A Summary of the Literature and a Report of Case With Autopsy Findings

R. J. Kressler, M.D., and E. E. Aegerter, M.D.
Philadelphia, Pa.

RECENTLY we have had the opportunity to study a case presenting a peculiar physical appearance, enlargement of the liver and spleen, skeletal deformities, and clouding of the corneas. On searching the literature, we have found reports[1-8] of 18 cases, the appearance and symptoms of which are all remarkably similar. This syndrome has been given the name of gargoylism by Ellis, Sheldon, and Capon[6] in an excellent report in which they presented seven new cases and reviewed ten from the literature. Diagnosis of two of their cases, those selected from Ruggles' series, are not included in this summary because in communication with Dr. Ruggles we find that the x-ray pictures were not typical of other cases of the syndrome.

Hurler[1] described the first case in 1919, and the brain was subsequently studied and reported by Tuthill[9] as a case of amaurotic familial idiocy.

In a recent communication Ashby, Stewart, and Watkin[8] have described one new case, in a sister of one of the patients previously described by Jewesbury and Spence in 1921.[2] They present autopsy findings and suggest the name of Hurler's disease for this syndrome.

Because we believe this disease to be not exceedingly rare and because there is almost nothing in the American literature concerning it, we are presenting this additional case which we have studied as completely as possible together with a summary of the unquestionable cases previously reported and have made a comparison of our autopsy findings with those of Tuthill and Ashby and coworkers.

CASE REPORT

P. M., male, eight and one-half years old, was born of healthy, unrelated Italian parents. Delivery was normal and spontaneous. At birth the child seemed normal in every respect. The birth weight was eight and one-half pounds. He was the fifth child; four brothers and one sister are living and well. He was breast fed until the age of four months when some vague gastrointestinal disturbance necessitated weaning; since that time the child has had intermittent paroxysmal attacks of nausea and vomiting. At the age of four and one-half months he developed pneumonia from which he recovered uneventfully. A congenital hydrocele was repaired at the age of three months. When the child was approximately five months

From the Departments of Pediatrics and Pathology, Temple University.

of age, the parents noticed a peculiar cloudiness of the corneas, beginning around the periphery but gradually involving the entire corneal area. In the first few years of life this disturbance did not seem to affect the eyesight, but later there was definite visual impairment. At six months the parents were told the child had rickets.

The patient showed definite tardiness in development. He did not sit up unsupported until two and one-half years, nor walk alone until three and one-half years; the first tooth did not erupt until four years; the anterior fontanel closed only between three and one-half and four years; he did not speak until about the fourth year. At the time of his first admission he had a very small vocabulary and enunciated poorly. He had never been able to raise his arms above the shoulder level, and he walked with a waddling gait.

The child was first seen by us at six and one-half years. He was short in stature and poorly nourished. The musculature was flabby. The features were heavy and peculiarly grotesque. The scalp hair was fine, but the eyebrows were thick and coarse. The bridge of the nose was shallow, and the nasal passages were filled with a thick, purulent discharge. The teeth were poorly developed and widely spaced. Both corneas were cloudy. A 45-degree abduction deformity was evidenced in both shoulder joints together with a 30-degree extension deformity in the elbow joints. The wrist and phalangeal joints were normal. A mild lumbar kyphosis was present. The lungs and cardiovascular system were normal. The abdomen was markedly protuberant, and a small umbilical hernia was present. The liver and spleen were palpable two fingers' breadth below the costal cage. The genitals were normal. Both hip joints showed marked limitation of motion with only 25 degrees of flexion and extension. The knee joints showed a 10-degree extension and 45-degree flexion limitation.

In the ensuing two years there was a gradual enlargement of the liver and spleen until both were a hand's breadth below the costal cage. At the age of seven and one-half years he began having paroxysmal attacks of dyspnea with cyanosis and dependent edema. Efforts to check this train of events were unsuccessful. Roentgenologic examination of the cardiovascular system revealed marked enlargement of all chambers of the heart. The patient died of cardiac failure in December, 1936, at the age of eight and one-half years.

The laboratory studies during his last admission were as follows: red blood cells, 4.59 million; white blood cells, 7,500; hemoglobin, 12 gm.; normal differential cell count; platelets, 290,000; coagulation time, 3 min.; clotting time, 2½ min.; urinalysis, normal; Wassermann, Kline and Kahn tests, negative; sedimentation index, 11 mm.; blood sugar, 91 mg.; urea, 11 mg.; nonprotein nitrogen, 42 mg.; cholesterol, 121 to 141 mg.; calcium, 13.2 mg.; phosphorus, 5.8 mg. per 100 c.c. of blood. Total protein was 6.14; albumin, 3.34; globulin, 2.8 gm. per 100 c.c. of blood. Albumin-globulin ratio was 1.2. Icterus index was 8 units; direct van den Bergh test was weak, delayed; the indirect test, 0.25 mg. per 100 c.c. Mantoux test, 1:1000 and 1:100, was negative. Splenic puncture and muscle biopsy were negative for foam cells and glycogen.

The *x-ray examination* of the skeleton showed: (1) flattening and elongation of the sella turcica with no evidence of bone erosion; (2) that the mesial half of each clavicle was apparently normal, while the lateral half showed abnormal curvature and flattening together with a defective achromial end; (3) that the twelfth rib was absent bilaterally and there was a left seventh cervical rib (the cervical portions of the ribs were abnormally narrow); (4) that the glenoid fossae were poorly formed and abnormally shallow (the humeral heads were irregular and corner shaped); (5) a mild abnormal kyphosis of the spine at the level of the twelfth thoracic and first lumbar segments with an absence of normal kyphosis in the midthoracic section.

The texture of the tenth, eleventh, and twelfth thoracic and first and second lumbar segments was abnormal with dense layers involving the cephalic and caudal thirds of these bodies. (6) The acetabula were shallow and poorly formed in the same manner as the glenoid fossae. The femurs showed elongation of their necks, poorly formed heads, and valgus deformity.

Autopsy Findings.—The head was enlarged. There was a scaly dermatitis of the scalp. The ears appeared to be displaced caudally on the sides of the head. The forehead was low, the eyes widely spaced. Both corneae showed a diffuse, milky cloudiness. The bridge of the nose was depressed. The mandible had a very obtuse angle which markedly widened the lower one half of the face. The teeth were broad and short, the tongue wide and thick. There was a profuse growth of lanugo over the sides of the face, neck, shoulders, back, and extensor surfaces of the arms and forearms. The neck was thick, the shoulders narrow. There was a moderate kyphosis and protuberant abdomen (Fig. 1). There was no hair over the pubic region. There was pitting edema of the lower extremities extending to the groin. The scrotum and penis were edematous.

The peritoneal cavity contained about 500 c.c. of clear, sanguineous fluid. Both large and small intestines were greatly distended with gas. There was marked edema of the root of the mesentery. The retroperitoneal lymph nodes as well as those of the mesentery and mesocolon were uniformly enlarged, averaging about 2½ cm. in diameter. The capsules were smooth and pale; the cut surfaces were homogeneous, pink, and moderately soft.

The pericardial cavity showed no abnormalities. The heart was enlarged; it weighed 220 gm. and measured 10 cm. horizontally, 11 cm. base to apex and 6 cm. anteroposteriorly. The myocardium was notably pale but firm. The mitral valve leaflets had a scalloped appearance with thickening of the edges of the cusps. The thickened areas were deep orange in color. The edge of the posterior leaflet was especially thick and contained a deposit of calcium which extended down the chordae tendineae and involved the posterior muscle bundles. The tricuspid valve leaflets were thickened but showed no calcium nor pigmentation. There was a moderate amount of calcium at the base of the cusps of the aortic valve and some streaking of the ascending portion of the aortic arch with a deep orange color.

The pleural cavities were normal. The lungs were moderately congested, the bronchi and the distal centimeter of the trachea were filled with a thick, mucoid secretion. The larynx and thyroid showed no changes. The thymus was large, weighing 21 gm.

The liver extended well below the costal margin. It weighed 1,190 gm. The edges were rounded, the consistency firm. The cut surface was yellow and greasy, resembling the liver of advanced fatty metamorphosis. The gall bladder and bile ducts were healthy.

The spleen was enlarged. It weighed 140 gm. It was firm. The parenchyma was a homogenous, deep red color.

The pancreas appeared to be normal.

The adrenals were thin and unusually bright yellow. They weighed 4 and 4½ gm.

The kidneys were a little enlarged, the right weighing 80 and the left, 90 gm. They cut with some increased resistance but showed no scarring grossly.

The gastrointestinal tract was normal throughout. The testicles appeared to be healthy. The bone marrow showed nothing of pathologic significance.

The vertebrae showed no lesions grossly. The neck and head of the femur were normal in appearance, but the acetabulum was shallow (Fig. 2). The clavicle was perhaps a little shortened, measuring 7.8 cm.; the lateral one-half was flattened and abnormally curved (Fig. 3). The sella turcica was shallow and elongated anteriorly but not eroded (Figs. 5 and 6).

Fig. 1.

Fig. 2.

Fig. 3.

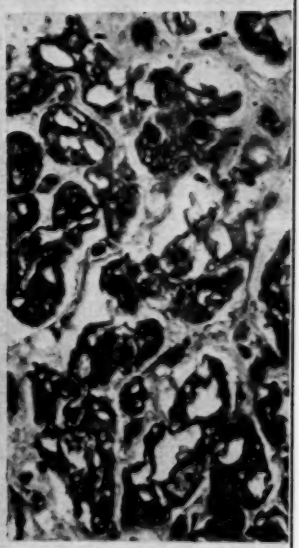

Fig. 4.

Fig. 5.

Fig. 6.

Fig. 1.—Photograph of patient on admission.

Fig. 2.—Roentgenogram of pelvis and femurs showing deformities of femoral heads and acetabula.

Fig. 3.—Roentgenogram of thorax showing deformity of shoulder girdle and ribs.

Fig. 4.—Photomicrograph of heart muscle (×675). Clear spaces in muscle cells are deposits of lipoid material.

Fig. 5.—Roentgenogram of skull showing deformity of sella turcica.

Fig. 6.—Picture of sphenoid bone sectioned longitudinally showing shallow, elongated sella turcica.

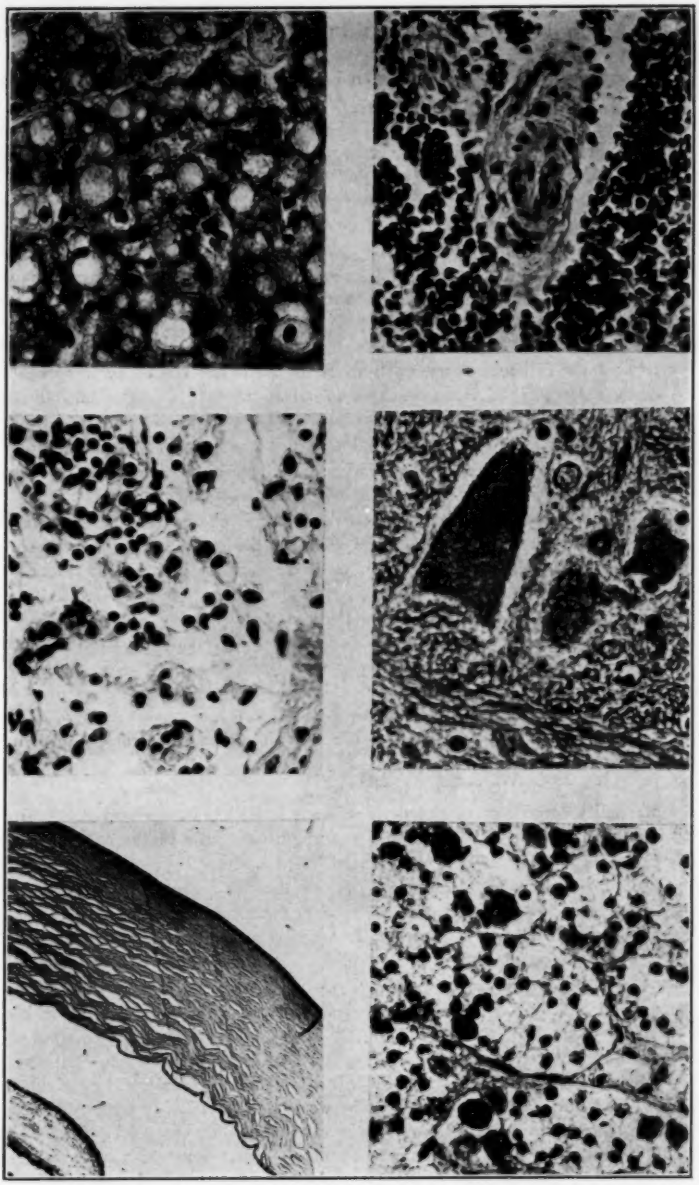

Fig. 7.—Photomicrograph of liver tissue (×675).

Fig. 8.—Photomicrograph of vessel in spleen (×675). Note thickening of vessel wall with infiltration of nonstaining substance.

Fig. 9.—Photomicrograph of section of lymph node (×675) showing deposits of lipoid material in lymph cells.

Fig. 10.—Photomicrograph of brain tissue (×675). The nerve cells are enlarged with thickening of their processes.

Fig. 11.—Photomicrograph of section of cornea (×40). The clear spaces may be caused by deposits of lipoid material.

Fig. 12.—Photomicrograph of section of the anterior lobe of the pituitary. Note the extensive infiltration into the three types of cells.

The brain weighed 1,200 gm. It was moderately enlarged and firm. The pituitary was definitely enlarged but normal in shape.

Microscopy: The nuclei of the muscle fibers of the heart were swollen, misshapen and stained unevenly. Much of the sarcoplasm was displaced by clear vacuoles in which apparently there had been an infiltrating substance (Fig. 4). The interstitial areolar tissue was increased in amount and showed vacuoles comparable to those seen within the muscle cells. The pericardium was thickened and here again were seen evidences of an infiltration, apparently between the cells.

The epithelial lining of the bronchioles was hyperplastic. The alveolar walls were immensely thickened; the capillaries were congested. In the wall and out in the lumina of the alveoli there were many cells approximately the size of plasmocytes with deeply staining, crescentic nuclei which were placed eccentrically. The remaining portion of the cell was taken up by a large vacuole. The alveolar spaces contained many macrophages, the cytoplasm of which was filled with multiple small, round vacuoles. The pleura was thickened and infiltrated.

Practically every parenchymal cell and many of the cells of the portal areas of the liver showed one or more vacuoles (Fig. 7). Some of these cells were so laden with this substance that there was almost no cytoplasm remaining.

A few of the lymphocytes in the spleen and some of the reticular cells of the secondary follicles showed vacuoles. The walls of the small vessels were markedly thickened and infiltrated (Fig. 8). Some of these were three times the thickness of the lumina. The infiltrating material appeared to be between the fibrous laminae.

The lymph nodes showed a very marked infiltration with a clear nonstaining substance. The sinuses and follicles about the periphery of the node were intact, but the parenchymal tissue in the center areas was almost completely replaced. Since much of this substance was between the cells, there appeared to be a great paucity of the latter. Most of the lymphocytes showed a large vacuole, many of them appearing as an oval ring of cell membrane with a flattened nucleus protruding from one side (Fig. 9).

The kidneys apparently escaped invasion.

The Hassall's corpuscles of the thymus showed degenerative changes. A few of the lymphocytes showed infiltration with a foreign substance in the cytoplasm.

The pancreas and thyroid appeared to be healthy.

The cells of the adrenal medulla had a very definite signet-ring appearance. It was extremely difficult to determine whether or not there was an excess of lipoid material in the cortical cells because of the varying amounts of this substance which normally occur there. A differential stain for lipoid material, however, showed no increase of this substance in these cells.

Both the lining cells of the convoluted tubules and the interstitial cells of the testes showed vacuolization.

The pituitary presented an interesting microscopic picture. The cells of the posterior lobe were apparently uninvolved, but there was extensive infiltration of the anterior lobe tissue. There appeared to be a normal ratio between the alpha, beta, and chromophobe cells, but the chromophobe cells were more extensively invaded than the other two types. This process was so marked that scarcely any normal chromophobe cells could be found (Fig. 12).

The bone marrow showed nothing of histopathologic significance. Microscopic examination of the bones revealed normal ossification and healthy bone growth.

The eye was fixed whole and sectioned longitudinally. The choroid, retina, iris, and lens appeared to be healthy. The anterior and posterior epithelial layers of the cornea were normal, but the laminae of the corneae proper were widely separated (Fig. 11). Whether this was an artifact secondary to fixation or the result of edema or infiltration is a matter of conjecture. The possibility of infiltration with

the same material that invades the other tissues should be considered. There was no cellular infiltration or other pathology to explain the corneal opacity observed during life.

We were particularly interested in the changes of the central nervous system since, to date, the brains of three other patients have been examined microscopically. Except for the adventitial thickening of the vessels and the evidence of tuberculous meningitis described by Tuthill, the brain of our patient closely paralleled that of his. Ashby and his coworkers gave an excellent description of the brain tissue of their first patient, and, except for the failure of the infiltrating substance to take stains in our case, their findings were identical with ours.

The nerve cells were greatly enlarged and balloon shaped with widening and distention of the axones and dendrites (Fig. 10). About the nuclei of many of these cells were clear, cresent-shaped areas which, when stained with sudan III, showed considerable quantities of lipide material. With special staining the Nissl bodies showed irregularities in size and shape and considerable degeneration.

It seemed imperative to us, after finding the outstanding etiologic factor to be an infiltration of an unknown substance into and between parenchymal and fibrous cells of practically all structures of the body, to determine the chemical nature of this substance. Since at autopsy the correct nature of the disease was unknown, no chemical analyses were performed on the gross organs. Hence, we were limited in determining the chemical nature of the infiltrating substance to histologic methods and the effect of polarized light. With hematoxylin-eosin and phloxine-methylene blue, the material appeared as clear spaces in tissues fixed in alcohol as well as those fixed in formalin and Helly's solution.

When frozen sections were made and stained with thionin the substance appeared as an opaque, gray material. The vacuoles remained refractile to staining with mucicarmine for mucine and with Best's carmine for glycogen. Routine fat stains and Nile blue sulphate were effective on only those sections of tissues which normally contain fat, and even here the large vacuoles remained clear. These results were not enhanced after mordanting. Phosphotungstic acid, Mallory's aniline blue and van Gieson's stains revealed a normal amount of connective tissue but did not stain the vacuoles. The Mallory-Heidenhain stain was ineffective as were the Davenport and Loyez stains for the complex cerebrosides. The substance was not doubly refractile to polarized light before or after heating. After reading the report of Ashby and his coworkers we reembedded some of our tissues in celloidin and again attempted to stain the infiltrating material but without success.

Consequently, we are still in ignorance as to the chemical nature of this material, but because of the similarity of this disease to the xanthomatoses, the appearance of the organs at autopsy, and the character of the infiltrating substance as seen in the thionin stained frozen sections, we believe the disease to be one of a metabolic dysfunction of one of the complex lipides.

DISCUSSION

Normally, the blood contains an emulsion of lipides, i.e., phosphatides, cerebrosides, and sterols. Deposits of these lipides may be found physiologically in certain tissues, namely, the suprarenals, testicles, ovaries, and nerve tissue. Of the idiopathic disturbances of lipide metabolism with characteristic clinical and pathologic manifestations, two groups have been described: primary xanthomatoses with abnormal deposits of fat and lipides normally found in the body, and those characterized by deposits of complex lipides not found normally in the body. Of the former, there is an acute and a chronic type. The

acute type, Niemann-Pick disease, shows several points in common with Hurler's syndrome (gargoylism), namely, the enlargement of the spleen, liver, and lymph nodes, ascites and edema of the lower extremities, visual disturbance, and progressive loss of the psychic function which may go on to complete idiocy of the Tay-Sachs type. Bone lesions are rare but do occur. Pathologically, an infiltration of the parenchymal cells with a fatlike material, including the anterior lobe of the pituitary and the lymphocytes in the blood stream, are found in Niemann-Pick disease. There are, however, definite points of differentiation which make it impossible to consider them as one disease. Niemann-Pick syndrome is fatal before the second year while many of the patients reported to have Hurler's syndrome are still living, many of them having reached adulthood. The bone changes are minimum and not of the same type radiologically. Large foam cells are the predominating histopathologic finding and the infiltrating material is mostly a phospholipide which takes fat stains after mordanting and shows anisotropic bodies with polarized light. Also the visual disturbance in Niemann-Pick disease is due to nerve tissue degeneration rather than to opacities of the corneae.

The chronic idiopathic xanthomatoses of the Hand-Schüller-Christian type and Hurler's syndrome have many points in common. The most important of these are dwarfism, bone defects, a nodular change in the endocardium of the heart valves, enlargement of the liver, spleen, and lymph nodes, hypogenitalism (lacking in our case), and lipide infiltration of the anterior lobe of the pituitary. But a close scrutiny of the two diseases reveals many widely differing characteristics. The plaques of the skin, the granuloma-like nodules of the viscera, and the exophthalmos so commonly seen in the Hand-Schüller-Christian syndrome are not found in Hurler's syndrome. On x-ray and histologic study the bone defects are found to be entirely different. The most notable feature of the Hand-Schüller-Christian syndrome is the presence of large foam cells which are entirely lacking in Hurler's disease. The infiltrating agent in the former is a mixture of cholesterol, cholesterol esters, phospholipides, and neutral fats, for which the tissues in our case gave negative reactions with the use of differential stains and polarized light.

In acute and chronic Gaucher's disease the infiltrating materials are a sphingogalactoside known as kerasin and alcohol-soluble phosphatides which, though they do not give the usual staining reaction for fats and lipides, will take a pale yellow stain after mordanting with potassium bichromate.[10] The infiltrating material found in our case was refractile to this treatment. A comparison of Gaucher's disease with Hurler's syndrome shows them both to be familial in nature with large

spleen, liver, and lymph nodes. Central nervous system changes are manifested in both. The diseases differ, however, in the lack of Gaucher's foam cells, conjunctival thickenings, pigmentation, and the hemorrhagic diathesis which are so often described in the late stages of Gaucher's disease.

The findings in the brain were peculiarly significant. Both grossly and microscopically the pathology here was compatible with that seen in the brain in Niemann-Pick disease. The central nervous system changes of the late infantile and early juvenile forms of amaurotic familial idiocy may also be identical.

Clinically, our patient showed clouding of the corneae which was sufficient to account for the symptoms of blindness. Unfortunately this clouding prohibited a study of the retina by the ophthalmologists so that they were unable to tell whether or not this structure showed the changes typical of amaurotic idiocy. However, microscopic sections of the eye did not show sufficient changes in the optic nerve and retina to account for the visual symptoms.

It may be concluded then that the brain in Hurler's syndrome is comparable with that seen in both amaurotic familial idiocy and in Niemann-Pick disease. Clinically, cases of Hurler's disease have not shown the epileptiform attacks nor decerebrate rigidity so often described with amaurotic idiocy, but it is noteworthy that the cases of Niemann-Pick disease with brain lesions do not show these symptoms either.

In 1929 Morquio[11] described a familial disease, the physical characteristics of which are remarkably similar to those of Hurler's syndrome. Indeed, of eight cases described by Ruggles,[4] two are unquestionably typical cases of Hurler's syndrome though they are not included in this summary because of insufficient clinical data. Since Morquio's report there have been several cases of this disease reported.[11-15] The physical appearance of these patients closely resembles those suffering from Hurler's syndrome, the chief difference being that they lack the degree of mental symptoms and the clouding of the corneae. This physical appearance is probably largely due to the characteristic bone lesions. But on x-ray study there is little evidence for the like comparison of these changes. It would appear therefore that the two are entirely different diseases.

Most of the cases of Hurler's syndrome reported to date have at one time or other been diagnosed as cretinism. The delayed mental development, the dwarfism, and the facies are not unlike those of this disease. But courses in thyroid therapy have never resulted in the usual improvement to be expected in cretinism, and, moreover, the

TABLE I

SUMMARY

CASE (AUTHOR)	AGE	SEX	BONE CHANGES				CORNEA	LIVER	SPLEEN	MENTALITY
			SKULL	SELLA TURCICA	SPINE	LIMBS				
Hurler	4½ yr.	M	enlarged; oxycephalic	large and shallow	kyphosis (lumbar)	Limitation of movement. Deformity of heads of humeri.	cloudy	enlarged	enlarged	sat up 1 yr; walked 26 mo.
Pfaundler	23 mo.	M	large	not examined	kyphosis (lumbar)	Not noted	cloudy	not enlarged	enlarged	retarded
Jewesbury and Spence	5½ yr.	M	brachycephalic	large and shallow	not noted	Limitation of extension at elbow	cloudy	not enlarged	not enlarged	retarded
Putnam and Pelkan	17 mo.	F	scaphocephalic	not noted	kyphosis (dorsolumbar)	Genu valgum	cloudy	enlarged	enlarged	retarded ?
Helmholtz and Harrington 1.	4½ yr.	M	scaphocephalic	not noted	kyphosis	Limitation of extension elbow, knee and fingers	cloudy	not palpable	not palpable	retarded
2.	2½ yr.	F	large	x-ray negative	kyphosis	Genu valgum	cloudy	enlarged	enlarged	retarded
3.	17 mo.	F	scaphocephalic	x-ray negative	kyphosis	Limitation of extension fingers	cloudy	enlarged	not palpable	retarded ?
4.	13 mo.	F	scaphocephalic	enlarged	kyphosis	Limitation of extension fingers	cloudy	examination unsatisfactory	examination unsatisfactory	retarded ?
Binswanger and Ullrich 1.	7 yr.	M	large		kyphosis	Limitation of motion of shoulder girdle and hips	cloudy	not noted	not noted	retarded

TABLE I—CONT'D

2.	1 yr.	M	large	large and shallow	kyphosis	Limitation of shoulder joint	cloudy	not noted	enlarged	retarded
Ellis, Sheldon, and Capon 1.	18 yr.	F	large jaw	large and shallow	kyphosis	Coxa valga; genu valgum; limitation of extension of joints	cloudy	enlarged	enlarged	retarded
2.	4½ yr.	F	oxycephalic	large and shallow	kyphosis	Genu valgum; limitation of extension of joints	cloudy	enlarged	enlarged	retarded
3.	4½ yr.	F	hydrocephalic	large and shallow	kyphosis	Limitation of extension of joints	cloudy	enlarged	enlarged	retarded
4.	3½ yr.	M	hydrocephalic	large and shallow	kyphosis	Limitation of extension of joints	cloudy	enlarged	enlarged	retarded
5.	1¼ yr.	M	brachycephalic	negative	kyphosis	Coxa vulga	cloudy	enlarged	not palpable	retarded
6.	11 mo.	M	brachycephalic	not examined	kyphosis	Atrophic changes at wrist	cloudy	enlarged	not palpable	retarded
7.	8 mo.	M	large and square	not examined	kyphosis	not examined	cloudy	not enlarged	enlarged	retarded
Ashby, Stewart, Watkin	3 yr.	F	brachycephalic	enlarged	angular deformity	Negative	not noted	not enlarged	not enlarged	retarded
Authors' case	8½ yr.	M	large	large and shallow	kyphosis	Limitation of motion of elbow, shoulder, and hip	cloudy	enlarged	enlarged	retarded

histologic study of the thyroid in our case in contrast to those studied by Ashby and his coworkers showed none of the changes found in severe hypothyroidism.

The infiltration into the anterior lobe of the pituitary with extensive destruction of all three types of parenchymal cells seen in our case should be sufficient to give rise to symptoms. But none of the cases of Hurler's syndrome reported have shown dystrophia adiposogenitalis, which usually accompanies hypopituitarism. However, dwarfism, the depression of the sexual function, and the peculiar changes in the skeleton might conceivably be caused by hypophyseal underactivity.

Von Gierke's disease may show an hepatomegaly early in childhood, but histologic study shows large quantities of glycogen in the liver and kidneys in one type and in the heart in the other[16] when stained by Best's carmine method after alcohol fixation. The tissues in our case showed no such reaction when so treated.

SUMMARY

We present a case showing a congenital, systemic disorder, the salient features of which are central nervous system lesions, hepatosplenomegaly, changes in the skeletal system, and corneal cloudiness. Microscopic study reveals an infiltration of a lipidelike substance in most of the tissues but chiefly in the liver, lymph nodes, and anterior lobe of the pituitary.

The etiology is unknown, but a metabolic dysfunction, probably of a complex lipide, appears to be the most likely cause. Infiltration of this material into the liver, spleen, heart, lymph nodes, corneae, pituitary, and possibly other endocrine glands probably accounts for the outstanding symptoms and signs. However, since the bone marrow in our case showed no infiltrative changes and since the bone lesions would seem more likely to be due to a defective germ plasm than an erosion, the skeletal signs remain unexplained.

A comparison with other diseases reveals nervous system lesions similar to those of juvenile amaurotic familial idiocy and Niemann-Pick disease and a lipide metabolic disturbance which resembles that of Niemann-Pick, Hans-Schüller-Christian and Gaucher syndromes. Consequently, we believe with Ashby and his coworkers that this disease should be classified as a fifth member in the category of lipidoses. Finally, though gargoylism is a short descriptive term, we feel that priority should be respected and that, since the other diseases of this group bear the names of those who described them, this disease should be called Hurler's syndrome.

We wish to acknowledge our indebtedness to Dr. R. W. Tyson, on whose service this patient was admitted, for assistance in the clinical interpretation of this case,

to Dr. W. E. Chamberlain for his cooperation in the x-ray studies, to Dr. L. W. Smith for helpful suggestions in the preparation of the pathologic report, and to Dr. Ernest Spiegle for his assistance in interpreting the histopathologic findings in the brain.

REFERENCES

1. Hurler, G.: Ztschr. f. Kinderh. **24:** 220, 1919.
2. Jewesbury, R. C., and Spence, J. C.: Proc. Roy. Soc. Med. **14:** 1, 1921.
3. Putnam, M. C., and Pelkan, K. F.: Am. J. Dis. Child. **29:** 51, 1925.
4. Ruggles, H. E.: Am. J. Roentgenol. **25:** 91, 1931.
5. Helmholtz, H. F., and Harrington, E. R.: Am. J. Dis. Child. **41:** 793, 1931.
6. Ellis, R. W. B., Sheldon, W., and Capon, N. B.: Quart. J. Med. **29:** 119, 1936.
7. Binswanger, E., and Ullrich, O.: Ztschr. f. Kinderh. **54:** 699, 1933.
8. Ashby, W. R., Stewart, R. M., and Watkin, J. H.: Brain **60:** 149, 1937.
9. Tuthill, C. R.: Arch. Neurol. & Psychiat. **32:** 198, 1934.
10. Rowland, R. S.: Brennemann's Practice of Pediatrics, Hagerstown, Md., 1937, W. F. Prior Company, Vol. 3, p. 15, chap. 23.
11. Morquio: Bull. Soc. de pédiat. de Paris **27:** 145, 1929.
12. Davis, D. B., and Currier, F. P.: J. A. M. A. **102:** 2173, 1934.
13. Brailsford, J. F.: Am. J. Surg. **7:** 404, 1929.
14. Burnett, E. J.: J. PEDIAT. **2:** 651, 1933.
15. Meyer, H. F., and Brennemann, J.: Am. J. Dis. Child. **43:** 123, 1932.
16. Ellis, R. W. B., and Payne, W. W.: Quart. J. Med. **29:** 31, 1936.

EHLERS-DANLOS SYNDROME

ALWIN C. RAMBAR, M.D.
CHICAGO, ILL.

EHLERS-DANLOS syndrome consists of the following symptoms: (1) hyperelasticity and hyperlaxity of the skin, (2) fragility of the skin and blood vessels, with cutting or splitting of the skin or the production of hematomas and pseudotumors following trauma, and (3) hyperflexibility of the joints.

Historically, the condition was first described by Ehlers[1] at a meeting of the Danish Dermatological Society in 1900. In 1907 Cohn[2] described a case of rubber skin (cutis laxa) with peculiar circumscribed skin changes, which he assumed to be related to each other. Danlos[3] in 1908, reported a case previously presented by Hallopeau and Macé de Lépinay, who had interpreted it as juvenile tuberous xanthoma. He contested their diagnosis and described the condition for the first time as an entity. Tobias[4] in 1934 reported the first case in the United States. Ronchese[5] has collected twenty-seven cases from the literature, including three of his own, to which I wish to add a further case.

REPORT OF CASE

H. L., a white male, four years old, was first seen two years ago. He was born prematurely at thirty-four weeks. His birth weight was 2,165 gm., an initial weight loss of 155 gm. was regained in ten days. No abnormalities of the skin or joints were noted at that time. At the time of his birth the mother was thirty years old, the father, sixty years old. There were two other normal children in the family. At ten months he was accidentally struck on the head and a large hematoma resulted which persisted for several months. He started to walk at eighteen months, and at this time his first cut occurred. Since then he has had many cuts, particularly of the forehead, scalp, arms, and legs. Bleeding was only moderate and stopped rapidly, even when the cuts were extensive. Sutures did not hold, and it was necessary to approximate the edges of the wounds with adhesive tape. His skin was pale, and felt soft and velvety. It could be stretched several times more than normal, and returned immediately to its usual position upon release. Subcutaneous tissue seemed to be absent, and the skin slid easily over underlying structures. The skin was disfigured by wide, irregular, atrophic scars wherever cuts had been. The shins were covered by areas of bluish and brownish pigmentation resulting from old bruises. Several molluscoid, empty raisinlike, pseudotumors were present over the elbows and knees.

Laboratory data showed red blood cells 4,030,000, leucocytes 7,900, lymphocytes 53 per cent, and polymorphonuclears—band 6 per cent, segmented 36 per cent, large mononuclears 1 per cent, eosinophiles 4 per cent. Coagulation time (capillary tube method) was 1 minute; bleeding time, 3 minutes. Blood calcium level was 10.29 mg., inorganic phosphates 5.6 mg. Blood Wassermann and Kahn tests were negative. Tuberculin tests with P.P.D. were negative. Roentgenograms of the long bones and the joints were normal.

From the Department of Pediatrics, Northwestern University, and the Sarah Morris Hospital.

Biopsy Specimen.—Sections of the skin showed the epidermis covered with a slight excess of keratin. The various layers of the epidermis in some fields are clearly recognizable. In other fields the epidermis seems atrophic, particularly the stratum corneum. The pigment layer also is not clearly recognizable. The papil-

Fig. 1. Fig. 2. Fig. 3.

Fig. 1.—Hyperelasticity of skin.
Fig. 2.—Scars on forehead and face.
Fig. 3.—Scarring and pigmentation of shins.

Fig. 4.—Photomicrograph of section of skin of knee, showing thinned epidermis and increased and irregular elastic fibers.

lary arrangement of the corium is accentuated in some regions. In other fields it seems absent. The outstanding changes in this region are the marked new formation of connective tissue and elastic fibers, which are brought out by the use of the van Gieson and orcein stains, respectively. Many elastic fibers are found very

irregularly distributed. They seem to extend in various directions and are often broken. Throughout the most superficial portion of the subcutaneous tissue, foci of lymphocytes and occasional polymorphonuclear leucocytes are discernible. Some of the vessels in this region show thickened walls and occasionally thrombi in some of the smaller arteries (Dr. Otto Saphir).

DISCUSSION

Many cases of cutis laxa alone have been reported, and cases of hyperelasticity of the skin with hyperlaxity of the joints without dermatorrhexis have been described.

Although fragility of the blood vessels is a prominent symptom, excessive bleeding at the time of cutting or splitting the skin does not occur. In one of Ronchese's cases[5] moderate bleeding is described, while in another bleeding lasted a long time. This child, however, suffered

Fig. 5. Fig. 6.

Fig. 5.—Linear wrinkling of forehead showing hyperlaxity of skin.
Fig. 6.—Hyperlaxity of joints.

from malnutrition and had been on a diet which was deficient in vitamin C. Capurro's patient,[6] a boy aged eleven years, had a severe nasal hemorrhage at seven years of age, but never bled excessively afterwards. Sézary's patient,[7] a twenty-four-year-old housemaid with extensive pulmonary tuberculosis, bled frequently from the gums and nose. In all of these instances it does not appear that bleeding has been an essential part of the syndrome.

Danlos[3] explained the tumor formation as the result of chronic contusions over bony prominences. If trauma causes an abundant circumscribed accumulation of blood, a pocket forms which may become infiltrated and later may be combined with an inflammatory reaction. Partial resorption occurs leaving a thin-layered raisinlike pseudotumor.

It is noteworthy that compression over these hematomas results in much more rapid resorption without tumor formation.

ETIOLOGY AND TREATMENT

Bielschowsky[8] has suggested a relationship to von Recklinghausen's disease because of the pigmentary deposits in the corium, which he found on biopsy, and Margarot[9] also mentions the possibility of this relationship, because of the presence of nevi and brownish spots in his patient. Brown patches and angiomas were mentioned in Capurro's patient.[6]

Capurro believed that the origin of the disease might be tuberculosis, as his patient had a positive tuberculin cutaneous test. Ronchese found a positive Mantoux test in two of his three patients, and Sézary's patient,[7] an adult, had pulmonary tuberculosis.

It is interesting to note that of this small group of patients reported, three have been prematurely born. Sézary's patient was born at seven and one-half months, weighing 1.93 kg. One of Ronchese's patients was an eight-month premature infant weighing 1815 gm., and my patient, as noted, was born at thirty-four weeks, weighing 2165 gm. However, it is unlikely that prematurity is an etiologic factor.

Ronchese concludes that little is known of the etiology and pathology of the condition, and considers the possibility of constitutional mesenchymatosis, endocrine disturbance, atavism, or an abnormal form of von Recklinghausen's disease.

Treatment consisting of various glandular extracts, and medications, has been of no avail. It is apparent that therapy must be directed toward protection against trauma, so that these patients can avoid all possible cuts and scars. Since the legs suffer the greatest damage in childhood, padded leather shinguards, similar to those worn by hockey goal tenders, have been made for my patient to provide increased security for him in his normal activities.

SUMMARY

A case of Ehlers-Danlos syndrome presenting the typical symptoms of hyperelasticity and hyperlaxity of the skin, fragility of the skin and blood vessels, and hyperflexibility of the joints is reported.

REFERENCES

1. Ehlers, E.: Dermat. Ztschr. **8**: 173, 1901.
2. Cohn, P.: Verhandl. d. deutsch. dermat. Gesellsch. **9**: 415, 1907.
3. Danlos, H.: Bull. Soc. franç. de. dermat. et syph. **19**: 70, 1908.
4. Tobias, Norman: Arch. Dermat. Syph. **30**: 540, 1934.
5. Ronchese, F.: Am. J. Dis. Child. **51**: 1403, 1936.
6. Capurro, R.: Arch. latino-am. de pediat. **20**: 713, 1926.
7. Sézary, A., Azérad, E., Miget, A., and Deparis: Bull. Soc. franç. de dermat. et syph. **40**: 1287, 1933.
8. Bielschowsky, F.: Deutsches Arch. f. klin. Med. **166**: 96, 1930.
9. Margarot, J., Deveze, P., and Coll de Carrera: Bull. Soc. franç. de dermat. et syph. **40**: 277, 1933.

1525 East Fifty-Third Street

THE SIGNIFICANCE OF SHIGELLA ALKALESCENS (ANDREWES)

A Clinical Appraisal of Nine Cases From Which the Organism Was Isolated

Paul V. Woolley, Jr., M.D., and Marian Sweet
Boston, Mass.

SHIGELLA alkalescens was described in 1918 by Andrewes,[1] who did not attach pathogenic importance to it, considering it only as an organism easily confused with the virulent dysentery types. Since then a few isolated reports of human infection have appeared in the literature. We wish to report a series of nine patients from whom this organism was recovered.

LITERATURE

The first report of human infection was made by Smith and Fraser[2] in 1928. They recovered the organism from the blood, stools, urine, and uterine discharge of a woman in the postpartum period. The autogenous strain was agglutinated in 1:480 dilution of the patient's serum. Her recovery was complete without specific therapy. Three years later Popoff and Spanswick[3] observed a patient with pyelonephritis during pregnancy and cultured the organism from the stool and urine. They demonstrated agglutinins in a dilution of 1:640 of the patient's serum. The organisms disappeared following abortion. In 1934 Starkey[4] recorded an instance of pyelitis with the *Shigella alkalescens* in the stool, blood, and urine. Agglutinating antibodies were not demonstrated but "precipitins" were present. The same year, MacKenzie and Ratner[5] noted another patient from whom alkalescens was recovered in the blood, stool, and urine. This patient showed evidence of severe septicemia and pyelonephritis but recovered after a severe course. The agglutination tests were not conclusive in this instance.

Murray and Pike[6] recovered the organism from the urine of an infant with acute pyelitis and found agglutinins to be present in the serum at a dilution of 1:640. The only epidemiologic report was made by Welch and Mickle,[7a] who studied an outbreak of mild dysentery among the students of an eastern university. *Shigella alkalescens* was recovered from the stools of all those infected as well as from a food handler who was symptom-free. These authors also studied four strains isolated from patients with chronic urinary tract infection. Weil,[8] in

From the Department of Pediatrics, Harvard Medical School, and the Infants' and Children's Hospitals, Boston.

Germany, has noted the organism in one patient with pyuria. Snyder and Hanner[9] have recently contributed another report of pyuria due to *Shigella alkalescens.*

BACTERIOLOGY

In morphology the *Shigella alkalescens* offers nothing to differentiate it from the remainder of the genus, being nonmotile, Gram-negative, and coliform in shape. The colonies are of average size after twenty-four hours' growth on agar, blood agar, or eosin-methylene blue plates, and they are round, smooth, translucent, and slightly elevated. In broth medium there is a rapid and uniform clouding with the formation of sediment on the second day. Acid is formed on Russell's slant without the formation of gas. Dextrose, maltose, mannite, arabinose, cellobiose, dulcite, xylose, and galactose are acidified readily. Rhamnose is fermented only after thirty-six hours' incubation. Lactose, sucrose, salicin, raffinose, and inosite remain unaffected. Dextrin and sorbite are utilized irregularly, the first of these being fermented readily by several of the strains studied in this series as well as by two strains obtained through the courtesy of Dr. H. Welch and Dr. F. L. Mickle. The reaction varies from neutral to strong alkalinity following complete growth in litmus milk. The methyl red test is positive, the Voges-Proskauer reaction negative, and indol is formed from peptone.

Immunologic studies by Welch and Mickle[7a] demonstrated an antigenic fraction common to alkalescens, and a majority of the Flexner strains. This is in accord with our observations since all of the strains were agglutinated in subtiter dilutions by polyvalent Flexner group sera. However, no one of the Flexner strains which we used was agglutinated by alkalescens serum, a phenomenon previously demonstrated by Welch and Mickle for both alkalescens[7a] and dispar.[7b] The same authors showed the close relationship of alkalescens and the Flexner types through the use of the Shwartzman phenomenon. All the strains secured from the patients in this series were agglutinated in low dilutions of high titer (1:10,000) typhoid sera, and again the typhoid organism remained unaffected in alkalescens serum.

Identification of the organism and its separation from the remainder of the mannite-fermenting dysentery group can be accomplished through the fermentation of dulcite and rhamnose, the neutral or alkaline reaction in litmus milk, the agglutination in subtiter dilution by polyvalent Flexner serum, and finally by the use of specific diagnostic sera. The routine procedures for the identification of this organism which we employ are as follows:

An organism giving the typical typhoid-dysentery reaction on the Russell slant is inoculated into dextrose, mannite, lactose, rhamnose, and saccharose. A broth tube is inoculated at the same time and allowed to remain at room temperature for the determination of motility at six, twelve, and eighteen hours.

	DEXT.	MANN.	LACT.	RHAM.	SACC.	MOTILITY
Typhoid	Ac	Ac	0	0	0	+
Flexner	Ac	Ac	0	0 (rarely Ac)	0	0
Sonne	Ac	Ac	Ac (late)	Ac	0	0
Alkalescens	Ac	Ac	0	Ac (36 hr.)	0	0

This preliminary separation is confirmed by the use of type specific Sonne and alkalescens sera (prepared by the injection of rabbits with increasing doses of formalin killed organisms), and commercial polyvalent Flexner and typhoid sera. The formation of indol is determined, but the reaction in litmus milk is not routinely investigated.

REPORT OF CASES

CASE 1.—R. D., six-and-one-half-year-old female. Diagnosis: Acute pyelonephritis. A child with irrelevant past and family history was admitted because of frequency of urination of one week's duration with drowsiness and fever for four days. The temperature had remained around 104° F. for the three days prior to entry, and mild abdominal pain had been present during the same period. There had been no similar complaints by other members of the household. The entrance examination showed her to be listless and to have a temperature of 104° F. There was marked bilateral costovertebral tenderness. The urine contained white blood cells, and there was a leucocytosis (13,500 per c.mm.) with 73 per cent polymorphonuclear forms. Pure growths of *Shigella alkalescens* were obtained in five cultures from the urine (catheterized) and three stool cultures. The temperature continued to range as high as 105° F. during the first five days in the hospital, and examinations of the urine, obtained by catheter, throughout the same period revealed many white cells. The fever abated on the ninth day of illness, but the pyuria persisted until the instigation of a ketogenic diet. No abnormalities were demonstrated by pyelography or kidney function tests. Two years after this admission she again acquired acute pyelonephritis with the colon bacillus as the offender. At the time of writing she is reported to be free from symptoms.

CASE 2.—B. E., five-month-old female. Diagnosis: Acute pyelonephritis. This previously well infant was admitted because of fever and fretfulness of one day's duration. Six days prior to entry she became irritable and refused her food. Following this she was in good health until the day of admission. Her physical examination revealed a temperature of 104° F. and extreme restlessness. The urine contained many white cells, and there was a slight trace of albumin. A moderate polynucleosis was present with a total white blood cell count of 14,000 per c.mm. She was acutely ill during the first nine days, and the temperature fluctuated between 100 and 104° F. while large numbers of white cells were present in all specimens of urine. Culture of the urine showed pure growth of *Shigella alkalescens* on three occasions, while a negative culture was obtained from the stools. The temperature returned to normal on the tenth day, but the pyuria persisted until after treatment with methenamine. Intravenous pyelograms were suggestive of a right hydronephrosis, but further investigation was deferred. She has been in good health since discharge, and the urine has been normal on several examinations.

CASE 3.—A. J., twenty-one-month-old female. Diagnosis: Acute pyelonephritis. This infant was admitted because of pain on urination and fever of ten days' duration. The past and family history was not contributory. The onset was sudden, and the fever, anorexia, and dysuria persisted for five days without change. During the next five days there was an increase in the severity of symptoms as well as con-

siderable abdominal pain. She appeared acutely ill at the time of admission with a temperature of 103° F. The urine contained many leucocytes, and the white blood cell count was elevated to 19,000 per c.mm., 70 per cent of which were polymorphonuclear cells. *Shigella alkalescens* was cultured from two specimens of urine as well as from the stools. She was acutely ill for six days, and the temperature remained between 100 and 104.5° F. The urine began to clear by the end of the first week in the hospital, and improvement followed. Intravenous pyelograms, cystograms, and kidney function tests were all within normal limits. Agglutinins against the organism were present in the serum at dilutions of 1:1280. The total period of hospitalization was four weeks, and she has been free from symptoms since discharge.

CASE 4.—L. McD., sixteen-month-old female. Diagnosis: Acute pyelonephritis. This infant was entirely well until three weeks before admission when she developed fever, listlessness, and irritability. These complaints persisted unchanged for two weeks and then increased in severity. Pyuria was found, and a course of methenamine given outside of the hospital without relief. She appeared pale but was afebrile at entry. The urine contained a large number of cells and *Shigella alkalescens* was obtained from it by culture. The white blood cells were not elevated in number. On the third day in the hospital the temperature rose to 103° F. Methenamine and ammonium chloride were given with excellent results. The urine cleared steadily, and she was discharged on the twenty-fifth day. Intravenous pyelograms and kidney function tests were normal. Agglutinins were not demonstrable in her serum, and the organisms were not recovered from the stools.

CASE 5.—L. M., eleven-year-old female. Diagnosis: Dysentery, Oxyuris infestation. The girl was admitted because of abdominal pain and vomiting of sixteen hours' duration. She had been well in the past, and there had been no similar complaints in the household. Three days before entry she had a mild diarrhea without other symptoms. She awakened with headache and dizziness on the day of admission, and these symptoms were followed by vomiting and abdominal pain. Abdominal symptoms became more marked during the course of the day, and the vomiting persisted. The temperature was 102° F. and the pulse rate 110. The abdomen was spastic and diffusely tender, the latter finding being confirmed by rectal examination. The white blood cell count was 26,000 per c.mm., and 90 per cent of these were polymorphonuclear forms. A laparotomy was performed, and a normal appearing appendix removed. Sections of this showed infestation with *Oxyuris vermicularis* but were without evidence of acute inflammation. The postoperative course was uneventful until the fourth day when the temperature suddenly rose to 104° F. and she passed seven watery green stools within a few hours. Culture of these showed *Shigella alkalescens* in large numbers. On the following day the temperature began to fall and the diarrhea to subside. The remainder of her stay was uneventful, and the organisms gradually disappeared from the stools.

CASE 6.—F. C., six-year-old male. Diagnosis: Enteric infection. This patient had been well until three days before entry. At that time he began to vomit and complain of intense abdominal pain which was cramplike in nature and severe enough to keep him awake at night. There were no deviations from the normal physical findings except for a temperature of 102° F. Laboratory data were not helpful until large numbers of *Shigella alkalescens* were found by stool culture. The fever abated on the fourth day of the illness, and the abdominal symptoms disappeared. Repetitions of the stool culture showed a constantly diminishing number of the organisms.

CASE 7.—E. A., six-and-one-half-year-old female. Diagnosis: Enteric infection. This girl was admitted because of vomiting and delirium of twenty-four hours' duration. She had been vaccinated ten days before entry, and a primary take had resulted. This caused her little discomfort, and she remained well until the onset of unusually severe and persistent vomiting. Her face was flushed at admission, she was completely disoriented, and there was severe ketosis. Laboratory data were not unusual except for large amounts of acetone in the urine. A lumbar puncture was made, and normal cerebrospinal fluid was obtained. Stool cultures showed an almost pure growth of *Shigella alkalescens*. After several intravenous infusions of glucose were administered, the temperature fell from 103° F. to normal within forty-eight hours. The ketosis also disappeared by the end of this period, and orientation was reestablished. The stool cultures continued to show *Shigella alkalescens* for several weeks, always, however, in diminishing number. Agglutinins were demonstrable in her serum for both the autogenous and stock antigens, a titer of 1:320 being reached during the fourth week. The Flexner antigens were not affected.

CASE 8.—M. L., ten-month-old male. Diagnosis: Dysentery. This infant was admitted because of diarrhea and vomiting of seventy-two hours' duration. There had been a questionable exposure to contaminated drinking water ten days before the onset of symptoms. Three days prior to entry he began having liquid green stools and vomiting. These symptoms persisted until admission. Physical findings were essentially those of dehydration and ketosis. The white blood cell count was 9,800 per c.mm., and there was a slight lymphocytosis. The stools gave a chemical test for blood even though none was found microscopically. Fluids were provided parenterally during the first week because of the persistence of vomiting and diarrhea. Large numbers of *Shigella alkalescens* were recovered from cultures of the stools during the diarrheal period, but these rapidly disappeared with the subsidence of symptoms. Agglutinins were demonstrable in dilutions of only 1:40 of the patient's serum.

Case 9.—B. W., twenty-year-old female. Diagnosis: Acute enteritis. A nurse on ward duty was suddenly stricken with diarrhea and vomiting. Laboratory data and physical findings were within normal limits. Large numbers of *Shigella alkalescens* were obtained from several cultures of the stools. The vomiting ceased after twenty-four hours, but the diarrhea persisted for three days. Agglutination tests were not made.

Three other strains have been recorded in this laboratory. Two were from patients with chronic pyuria in whom this species occurred as a transitory or secondary invader. In one of these the streptococcus appeared to be the primary offender, while it was the colon bacillus in the other. The third strain was sent to us for identification by a neighboring hospital. It had been recovered from the urine of a forty-year-old woman with postoperative pyelitis. The organism was cultured several times before a satisfactory response to methenamine therapy was obtained.

DISCUSSION AND SUMMARY

This series, while composed of only nine cases, represents a larger number than heretofore reported and brings out several important features. Four of these patients represent instances of infection of the genitourinary tract with the organism appearing in the urine in

pure culture. The case reports in the literature are primarily instances of genitourinary infection rather than gastrointestinal disease such as we ordinarily associate with the paradysentery organisms. During the same period of time over which these patients were seen, there were thirty-seven cases of dysentery, proved bacteriologically, admitted to the hospital. These were all due to either the Flexner or Sonne type. Only one of these showed evidence of pyuria, and repeated urine cultures failed to demonstrate the organism. Except for the cases enumerated in this paper, the dysentery organism was not obtained from any patient with pyuria admitted over the same period of time.

The four cases herein reported were comparable in severity to the acute pyelonephritis seen in the same age group and due to the colon bacillus. Three of them were treated with either a ketogenic diet or methenamine, and all recovered without subsequent demonstrable damage of the genitourinary tract. Blood cultures were not taken in these cases, and there was no evidence of septicemia as described by other writers.

Reports in the literature consistently fail to prove the presence of gastroenteric disorders due to *Shigella alkalescens*. The one exception to this is the single epidemic we have mentioned above.[7a] Boyd,[10] in his extensive study of the mannite-fermenting group of bacilli, did not observe dysentery attributable to *Shigella alkalescens*. Two different sets of symptoms were presented by five of the patients in this series. Patients eight and nine suffered from profuse diarrhea, similar in severity to instances of mild dysentery due to other paradysentery types. In three of the other patients vomiting was an outstanding symptom and was severe enough in one instance to require repeated administrations of parenteral fluid to combat the ketosis. Abdominal pain was a prominent symptom and was severe enough in one case to suggest the need for laparotomy. The organism was present in large numbers in each of these patients during the height of the symptoms and then decreased with clinical improvement. Diarrhea was present in only one of the three patients. An agglutination test was made on only one of these three and was then positive in dilutions of 1:320. It is not justifiable to conclude from three cases that *Shigella alkalescens* is an etiologic factor in such symptoms; yet it should be emphasized that it was the only organism present to which the etiology could be attributed. Others of the enteric group do give rise to similar findings, and the more liberal use of stool cultures from such patients may establish the fact of the pathogenicity of the *Shigella alkalescens*.

In the past we have regarded patients harboring *Shigella alkalescens* in the same light as those from whom indisputably virulent species have been recovered, maintaining enteric technique and requiring nega-

tive stool cultures before release. This survey has modified our concept. The observations of Gilbert and Coleman[11] and of Brown and Anderson[12] have shown the organism to be widely distributed throughout the community. It is found in an appreciable portion of the population, and yet enteric symptoms are encountered but rarely. It would seem probable that the state of the host was of more importance than the presence of the organism. Our present tendency would be to regard it more as we do the Morgan bacillus, the group described by Fothergill,[13] and several other enteric organisms. They are all pathogenic at times but are encountered fairly frequently in the asymptomatic population. The single recorded epidemic suggests that certain strains are endowed at times with increased virulence and are then pathogenic for an appreciable percentage of individuals. The absence of further epidemiologic reports makes this possibility infrequent enough to be ignored so far as individual carriers are concerned.

SUMMARY

A description of *Shigella alkalescens* has been presented, with an outline for its detection and differentiation.

In comparison to the remainder of the paradysentery group this form has a predilection for the urinary tract rather than being the cause of clinical dysentery. Its presence should be considered in any case of urinary infection due to a mannite-fermenting member of the dysentery group.

Occasional cases of mild dysentery are attributable to the species.

The organism was recovered from the stools of three children with abdominal pain and severe vomiting.

Gastroenteric symptoms are infrequent, and an appreciable portion of the population harbor the organism. It would therefore seem unnecessary to isolate the individual carrier except in the rare instance of an epidemic or during hospitalization.

REFERENCES

1. Andrewes, F. W.: Lancet 1: 560, 1918.
2. Smith, J., and Fraser, A. M.: J. Path. & Bact. 31: 511, 1928.
3. Popoff, N. W., and Spanswick, M. P.: J. Lab. & Clin. Med. 16: 437, 1931.
4. Starkey, D. H.: Canad. M. A. J. 31: 42, 1934.
5. MacKenzie, D. W., and Ratner, M.: J. Urol. 31: 671, 1934.
6. Murray, M. F., and Pike, R. M.: Clin. Misc., Mary I. Bassett Hosp. 1: 68, 1934.
7. Welch, H., and Mickle, F. L.: (a) Am. J. Pub. Health 24: 219, 1934. (b) J. Infect. Dis. 50: 524, 1932.
8. Weil, A. J.: Zentralbl. f. Bakt. 12: 376, 1929 (orig.).
9. Snyder, N. L., and Hanner, J. P.: J. Infect. Dis. 60: 51, 1937.
10. Boyd, J. S. K.: J. Roy. Army M. Corps 59: 241 (331), 1932.
11. Gilbert, R., and Coleman, M.: Am. J. Pub. Health 24: 449, 1934.
12. Brown, M. H., and Anderson, E. A.: Canad. Pub. Health J. 27: 560, 1936.
13. Fothergill, L. D.: J. Infect. Dis. 45: 393, 1929.

300 Longwood Avenue

CARE OF THE SKIN OF THE NEWBORN INFANT— PREVENTION OF INFECTION

L. Howard Smith, M.D.
Portland, Oregon

THE problem of care of the skin of the newborn infant has been approached from many different angles. There is a difference of opinion as to just what should be done and just what should not be done in reference to skin care. One of the chief problems of lying-in hospitals is the prevention of skin irritation and skin infections. An irritated skin may readily become infected. Any procedure that will lessen the incidence of pyodermic lesions is most desirable.

The use of antiseptic oils and ointments has been an improvement in prophylaxis, according to many reports in recent literature: Chadwell,[1] Guy and Jacob,[2] Potter and Abel,[3] Beane,[4] and Sanford.[5]

Our first introduction to the method of nonoiling and nonbathing the newborn came through Dr. W. F. Patrick, pediatrician in charge of the nursery at the White Shield Home, Portland, Ore. In May, 1931, Dr. Patrick started the practice of not oiling and not bathing the newborn infants during their first two weeks of life and was so satisfied with the resulting appearance of the skin and the absolute freedom from skin irritations and infections that he has continued this procedure ever since, over six years.

Feb. 1, 1935, two and one-half years ago, we discontinued oiling and bathing the newborn infant at the Multnomah County Hospital. Previous to this, we had been using 1 per cent copper oleate on the skin of the newborn infants and had found a great reduction in the incidence of pyodermia. But with the new treatment, or no treatment at all, with 1,734 babies we have had only two cases of even suspicious pyodermia.

The technique is simply not cleaning the baby after birth, that is, the vernix caseosa is not removed. Excess blood is wiped off, but that is all. The skin is neither bathed nor oiled during the infant's stay in the hospital. Warm water is used to clean the buttocks following stools. Each day the clothing is changed, but the infant is not bathed or oiled.

Within twelve hours after birth the infant's skin is clean; the vernix has disappeared! Unless one has witnessed the phenomenon, this miracle does not seem possible. It would appear that if this greasy, slimy newborn infant, who looks as if he had been rescued from a sewer, were not immediately cleaned up, he would smell like a dead fish in twenty-

From the Department of Pediatrics, University of Oregon Medical School. Read before the Annual Meeting of Region IV of the American Academy of Pediatrics, Los Angeles, California, November 5, 1937.

four hours. What a contrast to behold him a few hours later looking fresh and clean.

The only areas to be watched are the axillae and groin, for, if the vernix caseosa has not "dried" in these areas, the skin may remain moist and show irritation.

We believe the great advantage of this procedure of not oiling or bathing the newborn infant, in regard to the prevention of skin infections, is the lessened handling of the infant's skin.

Another advantage is the nursing time saved. Time studies were made, and it was found that the average time required for the initial care of the newborn infant, "cleaned," was thirteen minutes, while the average time for "uncleaned" babies was eight minutes—a saving of five minutes. The average time required for "cleaned" babies' daily care (after birth) during their stay in the hospital was eight minutes, and that for the "uncleaned" babies was five minutes—a saving of three minutes. This saving of time, multiplied by twenty or thirty—the daily population in the nursery—means one to one and one-half hours of nursing time saved each day.

Other institutions are using this method of newborn infant care with equally beneficial results. Sanford reported his experience with 609 babies, only 10 per cent showing skin irritations and only one infant, pustules. Dr. B. W. Black, Medical Director of the Alameda County Institutions, Oakland, Calif., informs me that for the last nine or ten years they have not bathed their newborn infants for the first twelve to twenty-four hours.

Miss Beane,[4] Supervisor of the Obstetrical Department of the Multnomah Hospital, reported our first year's experience in the *American Journal of Nursing*. We have also found that the most satisfactory treatment for any skin irritation of the newborn infant, even when pyodermia is suspected, is not an antiseptic solution or ointment, but a powder. We have been using Taylor's powder.

Mercurous chloride	3 parts
Talcum	2 parts
Zinc oxide	1 part

SUMMARY

During the last two and one-half years 1,734 newborn infants have been cared for without any initial cleaning or bathing and without further bathing or oiling of the skin during their stay in the hospital (ten to fourteen days). The decreased incidence of skin irritations and almost total lack of pyodermia have been truly gratifying.

REFERENCES

1. Chadwell, O. R.: New England J. Med. **199:** 983, 1930.
2. Guy, W. H., and Jacob, F. M.: J. A. M. A. **102:** 840, 1934.
3. Potter, R. T., and Abel, A. R.: Am. J. Obst. & Gynec. **31:** 1003, 1936.
4. Beane, G. F.: Am. J. Nursing **36:** 1207, 1936.
5. Sanford, Hayworth N.: J. PEDIAT. **11:** 68, 1937.

MEDICAL ARTS BUILDING

GRANULOCYTOPENIA AND HYPERLEUCOCYTOSIS FOLLOWING SULFANILAMIDE THERAPY

G. R. Alpert, M.D., and Roy P. Forbes, M.D.
Denver, Colo.

THE current interest in sulfanilamide therapy justifies the report of a case exhibiting spectacular changes in the blood picture following administration of the drug.

B. G., an eleven-year-old girl, was referred by Dr. Fred C. Klopfenstein, of Boulder, Colo., on July 9, 1937. Previous to the present illness, which began eighteen months before admission, the patient was in good health. Pertussis at two years was the only childhood disease. In January, 1936, both knees became swollen and painful. Symptoms subsided in about a month to return two months later with involvement of both elbows. A tonsil-adenoid operation performed in July, 1936, was followed by temporary improvement, but in the fall both wrists became swollen. For eight months previous to admission the patient was confined to bed with progressive involvement of all joints of the extremities and the spine.

Fever, anorexia, weight loss, and progressive anemia accompanied the arthritis. Three months before admission the patient had two convulsions occurring at night. Sugar was present in the urine at this time. Small doses of insulin, two blood transfusions totalling 600 c.c., massage and hydrotherapy effected some improvement in her general condition, but the joint involvement and fever continued.

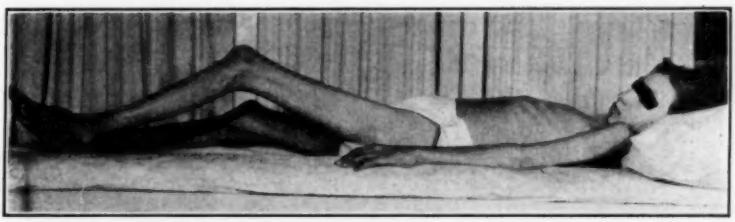

Fig. 1.—Photograph of patient taken shortly after admission.

On admission to Children's Hospital the patient presented the picture shown in Fig. 1. There was limitation of movement of nearly all of the joints, and the spine could not be flexed. Swelling of the second interphalangeal joints, wrists, elbows, and knees with some contractive deformity was noted. The spleen was palpable at the costal margin and later apparently enlarged to about 2 cm. below the margin. The heart was not enlarged, but a soft systolic murmur was attributed to the anemia. Accessory data from the laboratory included: red blood cells, 3,300,000; white blood cells, 9,600; polymorphonuclears, 71 per cent; lymphocytes, 26 per cent; eosinophiles, 3 per cent; hemoglobin, 47 per cent (Dare). Fasting blood sugar was 81; nonprotein nitrogen, 28.6; creatinine, 1.5; calcium, 10.5; phosphorus, 4.8; and cholesterol, 194 mg. The Wassermann reaction was negative. Two blood cultures were sterile in the febrile period. The sedimentation rate on July 17 was 32 mm. in sixty minutes. A throat culture revealed some colonies of *Streptococcus hemolyticus.*

From the Department of Pediatrics, University of Colorado School of Medicine, and Children's Hospital, Denver.

During the first four days in the hospital the temperature varied from 97° to 102° F. On the fifth day, July 13, we decided to give a course of sulfanilamide. The patient received 15 grains at 8:30 A.M. and 10 grains at 2 P.M. At 4 P.M. she complained of chilliness. A third dose of 15 grains was given at 5 P.M. At 5:30 P.M. the temperature was 102.8° F. when a blood count was done showing white blood cells 32,600 with polymorphonuclears 98 per cent. Emesis occurred at 6 P.M., and the face became very flushed. The temperature rose to 103.2° F. On account of nausea the patient received only 10 grains of sulfanilamide in the next twenty-four hours. On succeeding days 30, 20, 30, 30, 20 grains were given. During this period the leucocyte count dropped, but the percentage of neutrophiles remained high. The

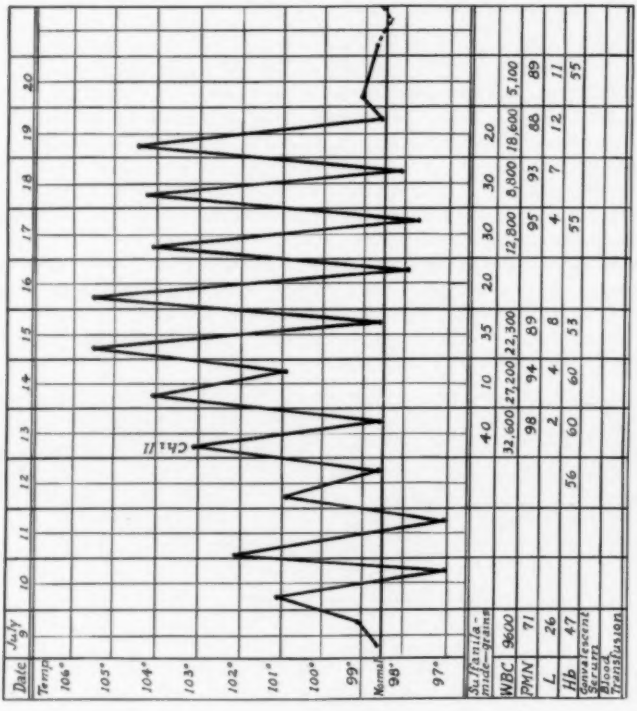

Chart 1.—Showing relationship of sulfanilamide therapy to hematologic findings. Dotted line indicates lapse of time.

temperature exceeded 105° on July 15 and 16 with daily remissions to normal, at which time the patient was usually quite drowsy. Chart 1 shows the essential hematologic findings. The patient received a total of only 185 grains (12.2 gm.) of sulfanilamide in seven days. The spiking temperature stopped abruptly at the same time that the drug was stopped and remained normal for one week. During this period there was relief from joint pains, and we felt greatly encouraged in this progress. On July 28 the temperature again rose and on July 29, 30 grains of sulfanilamide were given in doses of 10 grains at 9 A.M. and 2 P.M. and 5 P.M. A chill occurred at noon, or three hours after the first dose, and emesis at 2:30 P.M. and 8 P.M. A blood count taken after the first dose showed a total disappearance of granulocytes with the total count reduced to 3,200. Only three days previously, July 26, the count was white blood cells, 4,200; polymorphonuclears, 27 per cent; and

lymphocytes, 72 per cent. When the alarming report of the blood count was received, no more sulfanilamide was given, and for the first time we realized the full significance of the previous counts showing a gradual fall of the total leucocytes and granulocytes since the first day of sulfanilamide therapy. We had suspected the possibility of the hyperleucocytosis being related to the sulfanilamide therapy but had seen no such reactions recorded in the literature.

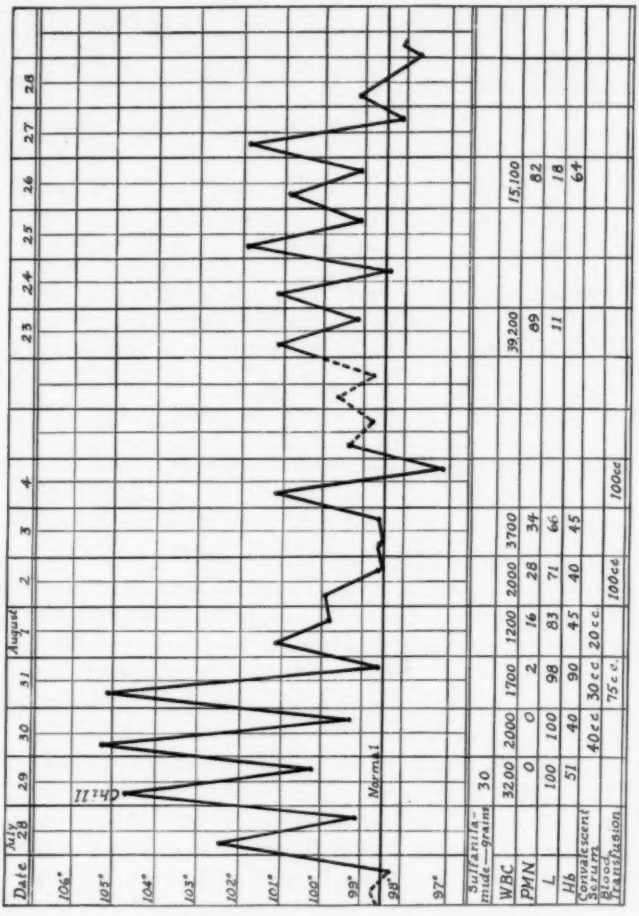

Chart 1.—Cont'd.

Fever remained high for three days, and an erythematous rash appeared on July 29 lasting for one day. This was followed a few days later by desquamation. That the rash was not due to sulfanilamide is suggested by a similar rash and desquamation which occurred during convalescence on August 19.

Oral lesions did not develop with the agranulocytosis, but a dry pleurisy requiring codeine and strapping of the chest occurred on August 1. Vomiting and abdominal distention were troublesome symptoms during this febrile period.

Treatment for the granulocytopenia consisted of three injections of convalescent streptococcus serum totalling 90 c.c., three small blood transfusions totalling 275 c.c., and four intramuscular injections of liver extract.

Improvement, both subjective and objective, was rapid during the month of August. Extreme and unaccountable fluctuations in the leucocyte counts were noted in this period. Thus on August 14 white blood cells were 15,000 with polymorphonuclears, 81 per cent. On August 19 in the morning the count was 79,400 with 78 per cent polymorphonuclears, but at 4 P.M. it was 16,600 with 78 per cent polymorphonuclears. It was on this date that the second erythematous rash appeared. The maximum temperature was 100.4° F. Counts of 31,800, 30,800, 33,200, and 39,200 were recorded on succeeding days. In the last week of hospital observation the blood picture returned to normal, a count of 12,200 with 77 per cent polymorphonuclears being recorded on September 1. The patient was discharged September 10. A vaccine containing a hemolytic and a nonhemolytic streptococcus recovered from throat culture was given by Dr. Klopfenstein over a period of months. By November the patient was able to walk unassisted.

COMMENT

As sulfanilamide contains the benzene ring, damage to the hematopoietic system may result from its administration. Severe hemolytic anemia, sulphemoglobinemia, methemoglobinemia, leucopenia, and leucocytosis have been reported as a result of sulfanilamide therapy. There have been several instances of severe stomatitis and death associated with agranulocytosis. In the case reported here, that of a chronic infectious arthritis, despite the fact that a leucopenia with 100 per cent lymphocytes developed, there was no complicating stomatitis, and the patient recovered.

Mitchell and Trachsler[1] report a case of Still's disease, or chronic infectious arthritis, in which, after the administration of large doses of prontylin, there developed a marked agranulocytosis, severe anemia, and a necrotic type of stomatitis and pharyngitis, followed by death. Long and Bliss[2] mention a case in which death followed a granulocytopenia combined with a bilateral, lateral and cavernous sinus thrombosis. The patient had received irregular medication with prontosil solution and sulfanilamide during the month before death. Plumer[3] had a case of subacute bacterial endocarditis, in which the white blood cell count before therapy was 26,000. After five weeks of prontylin therapy, the white blood cell count dropped to 400 with absence of neutrophiles on stained smears. The next day, on which death occurred, the white blood count was 1,600, blood culture positive for *Streptococcus viridans*, and there was an extensive gangrenous infection of the mouth and pharynx.

In the two cases reported by Trumper,[4] in which the pathologic findings were not as extensive as those above, the outcome was more favorable. In an adult with a septic mastoid, the white blood cell count was 18,000 with 85 per cent neutrophiles. After several days, treatment with prontylin and prontosil, the white cell count dropped

to 4,000 with 35 per cent neutrophiles. Withdrawal of the drugs was followed by high total and polymorphonuclear counts. In his other patient, a primipara, who after a stormy delivery, ran a febrile course with temperature ranging from 104 to 105° F., the white cell count was 20,000 with over 80 per cent neutrophiles. Prontylin and prontosil were given, and after a few days the total count fell to 6,000 with 50-60 per cent neutrophiles. The fever continued for six weeks, during which time the temperature ranged from 101 to 103° F., and the blood counts, made almost daily, were between 5,000 and 6,000. Two transfusions were given. Withdrawal of the drugs was promptly followed by a rise in the total count to 13,000 with over 80 per cent polymorphonuclears.

Hageman and Blake[5] report a series of specific febrile reactions due to sulfanilamide, during which a morbilliform rash appeared. During the "drug fever," the white cell counts varied between 7,000 and 48,000. No cases of neutropenia were noted in their series.

It is significant that in the cases of Mitchell and Trachsler, Long and Bliss, and Plumer the patients had received a considerable dosage of sulfanilamide over a period of many days, whereas in our case the patient received a relatively small amount of the drug. Furthermore, the hyperleucocytosis and subsequent leucopenia appeared promptly, suggesting an idiosyncrasy to the drug. Chills, nausea, and vomiting with the first dose are symptoms further suggesting an intolerance of sulfanilamide.

SUMMARY

A patient receiving comparatively small doses of sulfanilamide, exhibited striking variations in the blood picture, including total leucocyte counts and percentage of granulocytes. There was an apparent stimulation followed by a depression of hematopoiesis of the granulocytes.

REFERENCES

1. Mitchell, A. G., and Trachsler, W. H.: J. PEDIAT. **11**: 183, 1937.
2. Long, P. H., and Bliss, E. A.: Ann. Int. Med. **11**: 575, 1937.
3. Plumer, H. E.: New England J. Med. **216**: 711, 1937.
4. Trumper, A.: New England J. Med. **216**: 857, 1937.
5. Hageman, P. O., and Blake, F. G.: J. A. M. A. **109**: 642, 1937.

THE USE OF SULFANILAMIDE IN GONOCOCCAL INFECTIONS IN CHILDREN

JOHN W. HOLMES, M.D., J. ALBRIGHT JONES, M.D., AND NATHANIEL GILDERSLEEVE, M.D.
PHILADELPHIA, PA.

INTRODUCTION

THE study herein reported was made to determine the value of sulfanilamide in the treatment of gonococcal vulvovaginitis in girls or in gonorrheal urethritis in boys. The encouraging results of Dees and Colston[1] in forty-seven cases of various types of gonococcic infection in the male genital tract led them to believe that the drug would prove of great value. Believing that, in all probability, the drug would be given wide use in isolated cases of gonococcic infection, we considered that an attempt should be made to establish or deny its value in gonococcal vaginitis. Incidentally, four male children coming to the children's clinic were treated.

PLAN OF STUDY

1. All of the children were treated either in the clinic or gonorrheal ward of the Philadelphia General Hospital.

2. The children were all under 12 years of age, the boys being from 2 to 8 years old.

3. Physical examination preceded the use of the drug in every case.

4. The ward cases were carefully observed for any untoward effects, while in the clinic the mother was warned to stop medication upon appearance of any illness or mild complaints such as nausea, vomiting, vertigo, or rash. She was requested to bring the child to the hospital if necessary.

5. Weight, temperature, and general condition were checked at each weekly clinic visit, at which time smears were taken.

6. In most cases blood counts were taken at the beginning and completion of treatment. These at first included differential counts, but since no appreciable change occurred this was omitted later to lighten laboratory work.

7. Weekly smears were taken from deep in the vagina and were checked by two observers.

8. No local treatment except external cleansing with boric acid solution, or soap and water, was ordered.

9. In all patients receiving the drug orally, approximately 0.6 gm. of sulfanilamide daily per 20 pounds of body weight was used. This

From the Pediatric Department of the Philadelphia General Hospital.

amount was given in divided doses throughout the day. No attempt was made to use larger doses as most of the patients were ambulatory and were seen only once weekly. We felt that in dealing with children with a local condition, and not acutely ill, we were not justified in pushing the drug to a high blood concentration. We felt that if this drug is to have any value in vulvovaginitis it should be effective in safe doses.

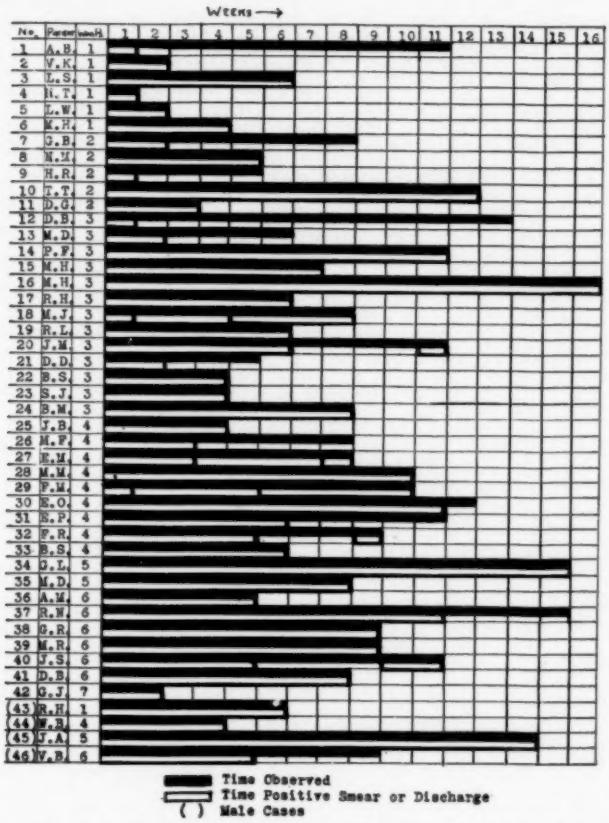

Chart 1.—Graph showing results of sulfanilamide orally in childhood gonorrhea.

10. Blood concentrations of sulfanilamide were determined in twelve patients who had received the drug three consecutive weeks. The determinations were made by using the method of Marshall,[2] by J. G. Reinhold, director of the Biochemical Laboratory of the Philadelphia General Hospital.

11. Suppositories containing 20 grains of powdered sulfanilamide in cocoa butter were used in a small group of cases.

RESULTS

Vulvovaginitis Treated by Oral Sulfanilamide.—The results of the treatment of forty-two cases of vulvovaginitis are shown in Chart 1. The first two columns show the number and initial of the individual cases treated, the last four, in parentheses, being the male patients. The third column indicates the total number of weeks of administration of the drug. In Chart 1, the solid bar represents the time in weeks during which the child was followed. The open bar represents the time in weeks during which the gonorrhea was considered active as evidenced by failure to obtain three smears negative for gram-negative diplococci with no vaginal discharge.

In most cases the smear and discharge coincided. Of the 20 cases in which one of the two persisted alone, 16 showed persistent positive smear with no visible discharge.

Of the entire 42 patients only 16 were relieved to the point of being able to return to school, having satisfied the Board of Health requirement of having three consecutive negative smears without vaginal discharge. Of these 16, 8 had recurrences of either positive smear or discharge within from two to six weeks. Thus only 8 patients of the 42 remained as candidates for cure. Only one of these has been followed for a period of three months.

TABLE I

SULFANILAMIDE ORALLY IN VULVOVAGINITIS

TOTAL NUMBER OF WEEKS OF TREATMENT RECEIVED	TOTAL CASES	NUMBER OF CASES UNRELIEVED	NUMBER OF CASES RELIEVED*	NUMBER OF CASES RECURRED
Less than 1	1	0	1	0
1	5	5	0	0
2	5	3	2	0
3	13	9	2	2
4	9	4	2	3
5	2	2	0	0
6	6	3	1	2
7	1	0	0	1
	42	26	8	8

*Bureau of Health requirement of three consecutive negative smears without discharge.

The proportion of the patients relieved to those in whom smears or discharge were persistently positive to the total number of weeks of treatment is shown in Table I. It is noted that one patient who had seven weeks of treatment, had a recurrence, while one having less than one week became negative and remained so for the eleven weeks observed. The proportion of cases unrelieved did not appear to decrease significantly with increased length of treatment.

In comparing the results of the chronic cases with the acute cases and with one month as an arbitrary dividing line, it is noted that, while negative smears were obtained more readily in the chronic cases, recurrences were much more frequent. A tendency for positive smears to be obtained with more difficulty in the chronic cases was noted, making relief more uncertain.

TABLE II

SULFANILAMIDE BY MOUTH

TYPE CASE	TOTAL	UNRELIEVED	RELIEVED	RECURRED
Acute	16	13	3	0
Chronic	13	5	3	5
Uncertain*	13	8	2	3

*Court cases sent in without history.

Three out of four male patients showed persistence of positive urethral smear and discharge during and following from one to six weeks of treatment with sulfanilamide orally. One case became negative after five weeks' treatment and at the end of three months had had no recurrence of discharge. He had had discharge for a month before coming to clinic.

TABLE III

SULFANILAMIDE BY MOUTH

PATIENT	WEIGHT	DAILY DOSE (GM.)	BLOOD LEVEL MG. %	RESULT
D. B.	47	1.6	1.1	Relieved
S. J.	51	2.0	1.9	Unrelieved
D. G.	36	1.3	9.0	Unrelieved
W. B.	30	1.0	3.5	Unrelieved
R. H.	40	1.3	0.1	Unrelieved
V. B.	49	1.6	1.9	Unrelieved
M. F.	31	1.0	2.0	Relieved
M. J.	61	2.0	2.1	Recurred
G. J.	71	2.0	2.4	Recurred
G. L.	60	1.6	2.5	Unrelieved
F. M.	81	2.3	1.3	Recurred
R. N.	32	1.3	0.5	Relieved
J. S.	31	1.0	2.7	Recurred

Blood Concentrations.—As shown in Table III, the level of sulfanilamide in the blood varied considerably with a dose of approximately 0.6 gm. per 20 pounds of body weight. Failures to clear up discharge or obtain negative smears were as frequent in those patients with high blood concentrations as in those with low levels of sulfanilamide in the blood. Indeed, one patient who achieved a concentration of 9 mg. per 100 c.c. of blood had a positive vaginal smear at the time the determination was made, after three weeks of treatment.

Toxic Symptoms.—In 29 patients blood counts were obtained before and after the administration of sulfanilamide over periods of from one

to eight weeks. No neutropenia, pseudoleucemia, or other significant changes appeared in the leucocyte counts. Most counts following treatment fell in the range between 6,000 and 9,000, the extremes being 4,400 and 25,000.

In 13 patients the erythrocyte count fell during treatment, 9 cases showing a fall of more than 500,000. However 16 patients had rises of similar proportions. In only one case did the red cell count fall below 3,500,000, the fall being from 3,740,000 to 3,060,000.

In 15 of the 29 patients the hemoglobin fell, the greatest loss being 3 gm., with an average loss of 1.3 gm. per patient. On the other hand 9 patients gained an average of 2.6 gm. of hemoglobin each.

No child developed pallor or hemolytic anemia clinically such as has been reported by Harvey and Janeway.[3]

Four patients showed weight losses of 1, 2, 2½, and 4 pounds, respectively. The remaining patients, excepting three whose weight remained stationary, gained from one to 10 pounds during the period of treatment.

Anorexia appeared as a complaint in four instances; headache in three; vertigo, drowsiness, and joint pain, in one. One patient developed a generalized, follicular erythematous rash starting on the face and hands during the second week of treatment.

In only one patient were toxic symptoms severe enough to cause alarm. This patient developed severe headache, vertigo, and anorexia on the second day of administration of the drug. She lost 2½ pounds during the illness but recovered promptly after the cessation of medication.

As a matter of interest it was noted that two patients in the hospital wards developed enuresis while taking sulfanilamide. On questioning mothers of clinic patients we found four more patients who had developed enuresis shortly after the drug was started. None of these patients had been troubled with enuresis before, although several had had vaginitis for fairly long periods. The symptom did not persist after treatment was stopped.

In no case did visible cyanosis or fever appear.

Treatment of Vulvovaginitis With Sulfanilamide Suppositories.—The suppositories were inserted at bedtime, each evening except the evening before the weekly smear was taken. Treatment was continued for a period of two weeks. A nurse inserted the suppositories with gloved finger, having cleansed the vulva first with boric acid solution.

In all five cases discharge persisted, smear remaining positive in four. As four patients developed vaginal irritation and bleeding following the use of the suppositories, and as no good results were obtained, the treatment was discontinued. In one patient the blood sulfanilamide was determined four hours after the insertion of the suppository and was found to be 1.04 mg. per 100 c.c.

COMMENT

The lack of important reactions is one of the interesting points in our series. Despite the frequency of cyanosis as reported, in no single instance was it found in our cases. No patient developed an alarming degree of anemia, nor was any tendency to develop anemia shown in the series as a whole. The weight curves showed little of importance. No definite change due to the drug could be noted. Several mothers reported the child's appetite was markedly improved after the drug was given, but no significance was attached to these statements. It is suggested, because our patients were ambulatory and healthy, that this may be a factor in the absence of toxic manifestations, although the drug was not "pushed" in any case.

As stated before, some of the cases were chronic, some acute. In the first group there would be little or no discharge, but positive smears would appear now and then. These patients for the most part had been coming to clinic for a long time and had had various local treatments.

Under what we considered a safe and adequate dosage, we feel that this drug has no value in the treatment of gonorrheal vulvovaginitis in young girls and has been disappointing in four cases of gonorrhea in male children.

SUMMARY

1. Sulfanilamide has been used in 51 cases of gonorrhea in children. These included 47 cases of vulvovaginitis in the female, and four cases of urethritis in the male. Five of the girls were treated by means of suppositories containing sulfanilamide, the balance having been given the drug by mouth.

2. Daily administration of 0.6 gm. of sulfanilamide per 20 pounds body weight gave practically no untoward effects of the drug.

3. Three out of four male patients failed to show any improvement.

4. The five patients with vulvovaginitis treated by suppositories containing sulfanilamide showed no improvement.

5. Of 42 patients with vulvovaginitis treated by sulfanilamide by mouth, only 16 were temporarily relieved, and of these, 8 had recurrences.

REFERENCES

1. Dees, John E., and Colston, J. A. C.: J. A. M. A. **108**: 1855, 1937.
2. Marshall, E. K., Jr., Emerson, K., Jr., and Cutting, W. C.: J. A. M. A. **108**: 953, 1937.
3. Harvey, A. M., and Janeway, C. A.: J. A. M. A. **109**: 12, 1937.

SIMULTANEOUS, BILATERAL, POSTDIPHTHERITIC, DIAPHRAGMATIC PARALYSIS TREATED BY MECHANICAL RESPIRATOR, WITH RECOVERY

A. Harry Neffson, M.D., and Samuel M. Wishik, M.D.
New York, N. Y.

BETWEEN the years 1916 and 1934 six reports,[1] totaling thirty-five cases, of postdiphtheritic paralysis of the muscles of respiration were published. Of these 35 patients only two were given artificial respiration, with recovery in both instances. Of the thirty-three patients who did not receive artificial respiration, twenty-four died, a mortality of 73 per cent. Three reports[1f, 2, 3] have appeared since 1933 describing the use of a mechanical respirator for postdiphtheritic respiratory paralysis. One,[1f] from this country, describes its use on two patients with paralysis of the intercostal muscles. The other two,[2, 3] from England, describe twenty patients also treated in this manner. Of these twenty-two patients, eight died, a mortality of 36 per cent. The deaths were due to circulatory failure in three, widespread pneumonia before use of the respirator in three, gangrene following recovery from the paralysis in one, and breakdown of the respirator preventing continuation of treatment in one case. The striking difference in mortality rates before and since the use of a mechanical respirator in this condition seems to prove the efficacy of this form of treatment.

Incidentally, it was noted that diaphragmatic paralysis occurred between the twenty-seventh and the fifty-sixth day of illness, and the paralysis lasted from four to fifteen days, usually about five days.

The following is the report of a case of recovery with the use of a mechanical respirator (Drinker) for widespread postdiphtheritic paralysis, with simultaneous, complete, bilateral involvement of the diaphragm and of the muscles of deglutition.

CASE REPORT

O. V., a six-year-old colored girl, was admitted to the Willard Parker Hospital on Oct. 2, 1934, with a history of sore throat, fever, and nasal discharge of four days' duration. No diphtheria immunization in the past or antitoxin during the present illness had been given. The past history was uneventful.

On admission the child appeared very toxic. There was a cervical adenocellulitis of the "bull-neck" type, and thick membrane in the nose and on the pharyngeal wall, tonsils, uvula, and soft palate. The child was given 30,000 units of diphtheria anti-

toxin, 10,000 intravenously and 20,000 intramuscularly. During the next four days she received 50 c.c. of 50 per cent glucose solution intravenously twice daily, each infusion being followed by injection of ten units of insulin. On the seventh day of illness, the urine showed four-plus albumin, two-plus acetone, three-plus sugar and from 10 to 15 white blood cells and from 5 to 8 red blood cells per high power field with an occasional granular cast. These urinary findings persisted during the following week. On the eleventh day of illness the patient began to speak with a nasal twang. The next day the first signs of cardiac damage became evident. The heart rate rose, the sounds became more distant with poor muscular quality of the first sound at the apex, and premature ventricular contractions appeared. Vomiting occurred several times. The electrocardiogram at this time showed a change in the character of the T-wave; from a previously normal curve it became diphasic in the first three leads. During the next three weeks all the heart findings became more pronounced. The liver edge could be felt two fingerbreadths below the costal margin. The nasal voice persisted. Repeated blood pressure readings fluctuated between 80/52 and 72/40. Vomiting occurred occasionally during this period.

On the thirty-fifth day of illness the child said she saw double. This disappeared in two days. At this time, coughing and vomiting followed the child's attempts to eat. This became so severe that feeding by nasal gavage had to be instituted the next day. Extreme lassitude set in. The attending neurologist, Dr. Wortis, noted the following: "There is no diplopia, nystagmus, or pupillary reflex disturbance, but convergence is slightly impaired. Palatal movement and pharyngeal reflexes are gone. There is difficulty in swallowing which is followed by coughing. There is so-called 'hot-potato' speech. There is motor weakness of all extremities, particularly the left upper, also the muscles of the neck and trunk. This marked weakness has caused ataxia of the arm movements. All deep reflexes are absent. The abdominal and plantar reflexes are normal. The sphincters are not involved. The senses of pain, touch, and position are intact. The findings point to a widespread post-diphtheritic polyneuritis with motor manifestations."

On the forty-third day of illness, the patient suddenly became extremely restless and dyspneic, breathing at the rate of fifty times a minute. She was unable to count or cough when asked to do so. The breathing was entirely thoracic, the abdomen being held scaphoid and immobile and the diaphragm remaining elevated during inspiration. Breath sounds were greatly diminished throughout the chest. The child was placed in a mechanical respirator (Drinker) working at the rate of fifteen times per minute, with a negative pressure of twenty cm. of water. Because of the child's inability to swallow, her trunk was raised above the level of the head in order to encourage drainage of saliva out of the mouth, and suction with a rubber catheter was applied as often as necessary. Feeding by nasal gavage was continued because it was well tolerated, no regurgitation occurring. The motor of the machine was turned off during the gavage feedings in order to minimize aspiration in the event of vomiting. A Levine tube was kept in situ and was changed once a day, using alternating nostrils. On the fifth day after being placed in the respirator, the patient was in a very poor condition. She was difficult to arouse, and signs of peripheral polyneuritis were more marked. From the next day on, however, she began to improve so that on the tenth day after being placed in the respirator she was able to remain out of it for one-half to one hour before becoming dyspneic. A week later she was weaned from the respirator by gradually decreasing the negative pressure, by allowing her to remain out of it for longer periods, and then, by keeping her out by day, but putting her back at night. Twenty days after the onset of the diaphragmatic paralysis the respirator was no longer required. She gradually regained her ability to count, cough, and swallow.

Inversion of the T-wave in the second lead of the electrocardiogram persisted until the forty-seventh day of illness. From then on there was gradual improvement in its contour, and by the sixty-eighth day of illness it returned to normal.

Nose and throat cultures were consistently positive for Klebs-Löffler bacillus during the early weeks. On admission there was a normal red blood cell count and hemoglobin with a polymorphonuclear leucocytosis. Later, a secondary anemia developed. This improved during her convalescence.

The patient was discharged from the hospital on the eighty-third day of illness with clear and sustained speech, easy breathing, both abdominal and thoracic, slow, regular, and strong heart action, complete muscle power in all extremities and the trunk, and with the return of the deep reflexes. She had made a complete recovery.

REFERENCES

1. a. Marriott, W. McK.: J. A. M. A. 75: 668, 1920.
   b. Mixsell, H. R., and Giddings, E.: J. A. M. A. 77: 590, 1921.
   c. Alesen, L. A.: J. A. M. A. 84: 730, 1925.
   d. Regan, J. C., and Guiness, A. B.: Am. J. Dis. Child. 33: 610, 1927.
   e. Samson, J. B.: Brit. M. J. 1: 895, 1934.
   f. Gordon, J. E., Young, D. C., and Top, F. H.: J. Pediat. 3: 580, 1933.
2. Mitman, M., and Begg, N. D.: Lancet 1: 1438, 1935.
3. McSweeney, C. J.: Lancet 2: 1093, 1936.

152 East Ninety-Fourth Street

46-55 157th Street, Flushing, L. I.

ACTIVE IMMUNIZATION AGAINST PERTUSSIS WITH A FORMALINIZED VACCINE

MAURICE L. BLATT, M.D., I. M. LEVIN, M.D., AND I. E. SCHAPIRO, M.D.
CHICAGO, ILL.

IN A REPORT on the whooping cough cases occurring under our observation during the years 1931 and 1932, we attempted to evaluate dosage, methods of inoculation, and optimal intervals between injections of pertussis vaccine.[1] During that period, numerous reports seemed to demonstrate the efficacy of prophylactic vaccination with *Hemophilus pertussis*. The work of Cullotta, Harvey, and Gordon,[2] Sauer and Hambrecht,[3] Rich, Long, Brown, Bliss, and Holt,[4] Shibley,[5] and MacDonald and MacDonald[6] was accepted as establishing the specificity of the Bordet-Gengou organism as the etiological agent.

From our own experience and the reports of other observers, we had reason to believe, when the present study was begun in December, 1933, that the prophylactic value of a pertussis antigen would be increased by a dosage much in excess of that commonly employed. Further, we thought that the local and constitutional untoward reactions, which had been observed and reported when large doses were used, might be obviated if the toxicity of the vaccine were modified by methods similar to those used in the conversion of diphtheria toxin to the toxoid, namely, by formalinization.

Justification for the institution of a formalinized pertussis vaccine to replace that of the heat-killed vaccine in common use seemed logical in view of the studies of Besredka,[7] who stated, "Heated to 55° C. for half an hour, the whooping cough endotoxin undergoes marked attenuation. Chloroform, toluol, thymol, and especially alcohol, deprive it of nearly all its activity. Filtration through a Chamberland candle retains the greater portion of the endotoxin. Heat modifies it so far as to render it incapable of causing local lesions. Heated whooping cough endotoxin, like heated plague endotoxin, does not vaccinate against non-heated endotoxin." We believed the toxic fraction of the vaccine to be of definite antigenic value and undertook means of preserving it. Furthermore, we thought that the failure of commercial vaccines in some instances might be caused by rapid deterioration of the antigenic properties of the vaccines and formalinization might aid in stabilizing these properties.

We are indebted to the Lederle Laboratories for technical help, manufacture and the supply of formalinized pertussis vaccine.

From the Cook County Children's Hospital, St. Vincent's Infant and Maternity Hospital, and the Pediatric Department, University of Illinois, Chicago, Ill.

In employing a heat-killed pertussis vaccine of a concentration of ten billion organisms per cubic centimeter, we had encountered difficulty because of autoagglutination. We realized that the conversion of toxins into toxoid had previously been successful only with exotoxin-producing organisms, of which the tetanus and Klebs-Löffler bacilli are good examples. No exotoxin had as yet been isolated from the *Hemophilus pertussis*. Nevertheless, it seemed worth while to attempt the evaluation of a vaccine modified by formalinization. At our suggestion, a process of formalinization was instituted by the Lederle Laboratories. The problem of autoagglutination was solved by certain mechanical changes in the method of vaccine preparation.

In all cultures of living organisms, a variable amount of autolysis takes place. It is probably caused by the development of some substance which liberates endotoxin by disintegration or frees exotoxin from the organism. Whether the formalin acts on a small amount of this free pertussis endotoxin or whether it produces changes in an exotoxin, as yet unidentified, is not certain.

Fifteen strains of *Hemophilus pertussis* were used in the production of our vaccine. These were maintained by culture on 30 per cent horse blood agar. Monthly tests for identity were made by agglutination with specific sera. Tests for hemolysis of blood agar and necrosis of the skin of a susceptible rabbit were also made (Pearl Kendrick[8]). As long as a culture was hemolytic and produced necrosis when 0.1 c.c. of a one billion suspension was injected intradermally into a rabbit, it was believed to be antigenic and suitable for vaccine production.

Cultivation of the stock strains on the 30 per cent horse blood agar tends to prolong these properties after isolation. When a batch of vaccine was to be prepared, the stock cultures were transferred to a liquid modified Bordet medium without blood. After forty-eight hours' incubation at 37.5° C., this was distributed over the surface of a solid agar medium. After further incubation, the growth was washed off the agar into sterile physiologic salt solution. The suspension was then smeared, gram stained, and examined microscopically for purity. To this suspension of living bacilli was added 0.5 per cent commercial formalin. This suspension was then incubated at 37.5° C. until 0.5 c.c. injected intradermally into a susceptible rabbit produced no necrosis and only a slight reddening without swelling. Filtration through sterile bolting silk and standardization of the number of organisms per cubic centimeter were then carried out. Sterility and safety tests were made. The stock suspension was standardized with sterile saline to a concentration of ten billion organisms per cubic centimeter, and phenol was added as a preservative. After another test had shown that this final suspension was sterile, it was placed in 20 c.c. vials for use.

PRIVATE PATIENTS

To determine the protective value of this pertussis vaccine, the children were divided into two groups. The total number of injected organisms in each group, approximately 30 billion, was given in the deltoid region. In the first group we employed three subcutaneous injections giving 0.5 c.c., 1 c.c., and 1.5 c.c. at weekly intervals. The second group was inoculated intracutaneously. The dosage used was 0.2, 0.4, 0.6, 0.8, and 1 c.c. The first three doses were given three days apart and the last two at four-day intervals. The latter method of administration was based upon the work of Besredka in emphasizing the rôle of skin reactivity in the development of resistance against certain specific infectious disorders. Tuft[9, 10] and his co-workers reviewed the literature and offered additional evidence to emphasize the rôle of the skin in immunology. They observed that intracutaneous inoculations were followed by a higher antibody response than subcutaneous or intramuscular. Furthermore, the incidence of local and constitutional reaction was definitely lessened by the use of the intradermal route.

We began the prophylactic use of this formalinized vaccine in our private practices early in 1934. No child with a history of exposure to whooping cough or with suspected or known whooping cough was included in the series.

The first group of 178 children, ranging in age from 6 months to 9 years, was inoculated as previously described. Fifty-four per cent of these children showed no local or constitutional reactions. In 40 per cent, local redness or infiltration occurred at the site of injection, and in 5.6 per cent there were systemic reactions of varying degrees. All patients with systemic disturbances also showed local reactions at the sites of injections. Elevation of temperature and irritability were interpreted as systemic reactions. In one child, 12 months old, severe reaction with high fever occurred at each inoculation. Only the first two injections were given. He is not included in Table I. There was no instance of cellulitis or abscess. With the same dosage for all age groups, no greater reaction was observed in infancy than in later childhood.

TABLE I

SUBCUTANEOUSLY INJECTED GROUP—178 PRIVATE PATIENTS (BEFORE EXPOSURE)

	REACTIONS				PERIOD AFTER COMPLETION OF IMMUNIZATION					
AGE	NO.	NONE	LOCAL	SYSTEMIC	UNDER 6 MO.	6-12 MO.	12-24 MO.	2-3 YR.	3-4 YR.	WHOOPING COUGH
6-12 mo.	92	68	19	4	9	18	31	26	7	2
12-24 mo.	11	3	6	2	0	0	0	11	1	5
24-36 mo.	16	7	8	1	0	0	1	10	4	3
3-6 yr.	35	11	22	2	0	0	1	20	15	3
6-9 yr.	24	8	16	1	0	0	2	17	5	1
Total	178	97	71	10	9	18	35	84	32	14

In this series, 9 children have been under observation for less than six months since completion of their inoculations. Eighteen children were observed from 6 to 12 months, 35 from 12 to 24 months, 84 from 2 to 3 years, and 32 from 3 to 4 years.

In this group of 178 patients, subcutaneously inoculated, whooping cough developed in 14 children, approximately 8 per cent. The interval between inoculation and the onset of the disease is shown in Table II. The shortest interval between pertussis and completion of inoculation was 13 days; the second shortest, 57 days. Four developed the disease after an interval of between 7 and 14 months, and 8 children became ill between 21 and 31 months. The disease was extremely mild in every instance but one, and there were no complications and no deaths. In this group of 178 patients, 92 per cent were apparently protected.

TABLE II

TIME RELATIONSHIP BETWEEN INOCULATION AND INCIDENCE OF PERTUSSIS IN 14 SUBCUTANEOUSLY INOCULATED PATIENTS

	AGE	INOCULATION COMPLETED	WHOOPING COUGH	PERIOD AFTER INOCULATION	NATURE OF DISEASE
1. B. B.	4 yr.	5/30/34	2/20/36	21 mo.	Mild
2. H. R.	2 yr.	7/30/34	4/13/36	21 mo.	Mild
3. S. L. T.	7 mo.	7/23/34	7/14/36	24 mo.	Mild
4. B. G.	3 yr.	10/ 5/34	8/28/36	22 mo.	Mild
5. G. G.	6 yr.	9/28/34	8/29/36	26 mo.	Mild
6. C. G.	14 mo.	10/ 5/34	8/28/36	22 mo.	Mild
7. C. L.	21 mo.	6/15/34	8/29/36	26 mo.	Mild
8. O. K.	8 yr.	9/10/34	11/ 1/35	14 mo.	Mild
9. T. K.	8 mo.	4/ 6/35	11/20/35	7 mo.	Mild
10. H. O.	4 yr.	10/ 9/34	5/12/37	31 mo.	Mild
11. B. S.	2½ yr.	5/28/36	6/15/37	13 mo.	Mild
12. L. L.	3 yr.	11/12/34	6/ 9/35	7 mo.	Mild
13. A. B.	16 mo.	1/ 1/35	1/14/35	13 days	Mild
14. W. G.	2 yr.	5/21/34	7/17/34	57 days	Severe

In the second group of 69 children in private practice (Table III), five intracutaneous injections of the vaccine were given. In this group, ranging in age from 6 months to 13 years, 81 per cent showed

TABLE III

INTRACUTANEOUSLY INJECTED GROUP. 69 PRIVATE PATIENTS (BEFORE EXPOSURE), ONE INCOMPLETELY INOCULATED

AGE	NO.	NONE	LOCAL	SYSTEMIC	OBSERVATION PERIOD					WHOOPING COUGH
					UNDER 6 MO.	6-12 MO.	12-24 MO.	2-3 YR.	3-4 YR.	
6-12 mo.	4	4	0	0	1	0	0	1	3	0
12-24 mo.	19	17	2	0	4	0	3	12	0	0
24-36 mo.	5	5	0	0	0	0	1	3	1	0
3- 6 yr.	31	23	6	1	4	0	2	13	12	4
6-13 yr.	10	7	4	0	4	0	0	4	1	2
Total	69	56	12	1	13	0	6	33	17	6

slight transient local redness without pain and were classed as having no reaction. Seventeen per cent reported local redness and swelling with sore arms. One child showed a systemic reaction. As with the subcutaneously inoculated group, there was no instance of cellulitis or abscess in these intracutaneously injected children. With the same dosage for all age groups, no greater reaction was observed in infancy than in later childhood. In this series, 13 children have been under observation for less than 6 months since completion of their inoculation. Six children were observed from 12 to 24 months, 33 from 2 to 3 years, and 17 from 3 to 4 years.

In the intracutaneous group of 69 children, whooping cough developed in 6, approximately 8 per cent. The interval between inoculation and the onset of pertussis is shown in Table IV. The earliest case developed 8 months after prophylactic injection; 5 others developed the disease after an interval of 22 to 34 months. The disease was moderately severe in all, but there were no complications and no deaths. In this group of 69 patients, 92 per cent were apparently protected, the almost identical figure for the subcutaneous group.

TABLE IV

TIME RELATIONSHIP BETWEEN INOCULATION AND INCIDENCE OF PERTUSSIS IN 6 INTRACUTANEOUSLY INOCULATED PATIENTS

	AGE	INOCULATION COMPLETED	WHOOPING COUGH	PERIOD AFTER INOCULATION	SEVERITY OF DISEASE*
N. L.	3½ yr.	7/30/34	5/19/37	34 mo.	Moderately severe
L. T.	18 mo.	11/28/34	3/ 9/37	28 mo.	Moderately severe
M. F.	4 3/12 yr.	2/23/35	12/25/36	22 mo.	Moderately severe
E. F.	5½ yr.	2/23/35	12/15/36	22 mo.	Moderately severe
A. M.	6 yr.	12/27/34	8/ 1/35	8 mo.	Moderately severe
B. T.	4½ yr.	12/15/34	8/ 9/37	28 mo.	Moderately severe

*No complications in these six patients.

A study of the reported incidence of pertussis in the age groups of children in the white population of Chicago was made in order to evaluate the effect of inoculation in the children of our private practices. The figures for 1934 show 461 reported pertussis cases in a census of 45,800 white children under one year of age. During 1935, 493 cases were listed in the same age group. Between the ages of 1 and 5 years (census 186,814), 2,374 cases were reported in 1934, and 2,160 cases were noted in 1935. In the age group of 5 to 9 years (census 254,934), 2,125 cases were reported in 1934 and 1,610 cases in 1935. From the ages of 10 to 14 years (census 268,423), 136 cases were reported in 1934 and 97 cases in 1935. From a population of

755,971 children under 14 years of age, 9,456 cases of whooping cough were listed during 1934 and 1935. It is a well-known fact that there is a wide discrepancy in the figures for the reported cases and the actual incidence of whooping cough. Therefore, the Department of Health statistics fall far below the true epidemic index.

TABLE V

INCIDENCE OF PERTUSSIS, CHICAGO, 1934-1935, IN INOCULATED PRIVATE PATIENTS AS COMPARED WITH THE REPORTED INCIDENCE IN SIMILAR AGE GROUPS IN THE GENERAL WHITE POPULATION[11]

PRIVATE PATIENTS				HEALTH DEPARTMENT REPORTED CASES (NOT ACTUAL INCIDENCE)*			
AGE GROUP	NUMBER	PERTUSSIS CASES	PER CENT	AGE GROUP	CENSUS (WHITE POPULATION) OF 1930	PERTUSSIS CASES	PER CENT
Under 1 yr.	40	0	0.0	Under 1 yr.	45,800	954	2.08
1-6 yr.	105	2	1.9	1-5 yr.	186,814	4,534	2.4
6-14 yr.	31	1	3.2	5-14 yr.	523,357	3,968	0.7
Total	176	3	1.7		755,971	9,456†	1.2†

*Health Department figures are fallacious for comparison because the total group includes patients inoculated at large, others who recovered from pertussis, and a *large undetermined* number, undiagnosed and unreported.

†These figures must be multiplied by the factor x, which represents the ratio of the actual incidence to the reported number.

In 1933 the reported incidence of whooping cough was 69.3 per 100,000 population. The percentage mortality was 0.7 (18 deaths in 2,487 reported cases). In 1934 there was a sharp rise to 165.4 per 100,000 and the percentage mortality was 1.1 (64 deaths in 5,772 reported cases). During 1935, 4,864 cases were reported to the Chicago Department of Health; an incidence of 139.3 per 100,000 population. In 1936 the reported cases rose to 5,925, an incidence of 169.3 per 100,000, and for the first six months of 1937 there were reported 1,759 cases, an incidence of 100.8 per 100,000 population.

A glance at the preceding figures points out the probable incidence of exposure of our private patients during the years 1934 to the latter half of 1937. The intimacy of their contact with pertussis, unrecognized and unreported, remains a conjectural figure.

Bearing these facts in mind, we cannot make a direct mathematical comparison of the percentage of incidence of whooping cough in the uninoculated children at large in Chicago and our group of inoculated private patients. The interpretation of Table III indicates a lower incidence in our private patients, as the reader multiplies the reported cases in the general population by his estimate of the factor x.

INSTITUTIONAL CHILDREN

In our private practices the children vaccinated had no history of exposure to whooping cough and were without suspected or known whooping cough. At St. Vincent's Infant and Maternity Hospital

and the Cook County Children's Hospital the children vaccinated were constantly directly or indirectly exposed to the disease. St. Vincent's Infant and Maternity Hospital houses 250 well infants and children from birth to three and one-half years of age. K. P., a female child, two and one-half months of age, in Ward C on the fifth floor, residing in the institution since birth, began to cough on June 3, 1935. There had been no instance of whooping cough in the hospital for two years. There was no demonstrable direct history of exposure to visitors; children being entirely excluded. Lack of recognition of pertussis in this child resulted in failure to institute measures of isolation and prophylaxis at once, and for twenty-six days she directly exposed 24 other children in the same ward. On the day the diagnosis was made, 3 other children in this room were sent to our observation ward on the first floor as well-advanced whooping cough patients. Through nurses and attendants circulating through all the wards, 50 other children on the same floor were indirectly exposed.

Twenty-five of the 74 exposed children received five intracutaneous injections of the formalinized vaccine. Three of the 74 were already in the active stage of pertussis and were transferred, as mentioned above. The remaining 46, not included in our series, received another type of vaccine. Thirty-one of the 46 developed pertussis. These children are mentioned only because they constituted an added, material source for the spread of pertussis organisms. No child in this group of 25 under investigation was coughing at the time the inoculations were started. Seven children of this group were in Ward C in direct contact with the first child to develop pertussis. She and her 7 immediate contacts remained together throughout her illness. Two of these patients, Cases 9 and 15, immunized over a period of 14 days, developed whooping cough 40 and 60 days, respectively, after completion of inoculation. They showed no signs of the disease within the 26 day preinoculation period and the 14 days of inoculation. However, pertussis occurred after a period which is as long as the usual course of average whooping cough. The other five, direct contacts, remained well (Table VI, Cases 21 to 25).

The direct exposure for a twenty-six-day period of this group of 7 children, all under 4 months of age, without the development of whooping cough, suggests a variability in the incubation period and demonstrates our inability to determine the exact time of infection. It also brings up the question as to what degree the virulence of the organisms and the level of natural immunity will influence the incidence of the disease.

Knoepfelmacher[12] quotes Finkelstein, Gottlieb and Moller, who reported incubation periods of three weeks to several months. He further states that in families with a large number of children not every

child always becomes infected, even though they all live together (silent immunization). A congenital immunity against the disease may be accepted. A. Friedlander[13] quotes the work of von Shally, Blum, and Smith, who studied the case records from a New York clinic and found that natural immunity to pertussis was exhibited by 31.6 per cent of families. Fifty-eight per cent of children in partially

TABLE VI

ANALYSIS OF RELATION OF EXPOSURE TO ONSET OF PERTUSSIS IN 25 VACCINATED CHILDREN (FORMALINIZED PERTUSSIS VACCINE). FIFTH FLOOR ST. VINCENT'S HOSPITAL

CASE	SEX	AGE (MO.)	DAYS OF INDIRECT EXPOSURE	DAYS OF DIRECT EXPOSURE	TOTAL DAYS OF EXPOSURE BEFORE ONSET OF COUGH	DAYS EXPOSED BEFORE INOCULATION	PERIOD OF INOCULATION (DAYS)	INTERVAL FROM COMPLETION OF INOCULATION TO ONSET OF COUGH (DAYS)
1. W. C.	M	8	11	34	45	26	14	5
2. M. K.	F	12	11	40	51	26	14	11
3. G. C.	M	8	11	44	55	26	14	15
4. T. O.	M	9	8	52	60	26	14	20
5. H. M.	M	10	11	54	65	26	14	25
6. R. M.	M	13	15	52	67	26	14	27
7. M. S.	F	13	11	58	69	26	14	29
8. J. D.	M	10	11	59	70	26	14	30
9. W. C.	M	4	0	82	82	26	14	40
10. S. N.	M	16	11	74	85	26	14	45
11. C. F.	M	10	11	74	85	26	14	45
12. V. F.	M	7	11	74	85	26	14	45
13. G. K.	M	10	11	74	85	26	14	45
14. P. S.	F	14	11	89	100	26	14	60
15. C. G.	M	4	0	102	102	28	14	60
16. M. M.	M	9	13	104	117	28	14	75
17. J. C.	M	11	10	20	30	14	Pertussis after one inoculation	
18. I. S.	M	10	0	30	30	14		
19. M. M.	F	11	0	15	15	14		
20. P. J.	F	11	0	75	75	14	14	No pertussis
21. A. F.	M	4	0	108	108	3	14	
22. D. W.	F	3	0	60	60	0	14	
23. S. B.	F	2	0	46	46	0	14	
24. J. H.	M	3	0	60	60	0	14	
25. P. L.	M	4	0	106	106	0	14	

Summary:

Pertussis in 17 completely inoculated patients
Pertussis in 2 incompletely inoculated patients
No disease in 6 patients

immune families escaped the disease after exposure. While they admit that their series was not large enough to warrant drawing sweeping conclusions, their findings are in accord with the generally accepted view that some degree of natural immunity to pertussis does exist. Our own experience seems to indicate a lesser degree of natural immunity than that found by von Shally and co-workers.

The failure to develop whooping cough in 5 of this group of 7 infants is particularly striking in view of the well-known fact emphasized by E. Feer[14] that "in no other contagious disease is infancy so frequently affected as in pertussis. Many children are attacked within the first few months. Indeed even congenital pertussis has been reported where the mother has had the disease before delivery."

Of the remaining 18 children in this group, 3, one aged 10 months and 2 aged 11 months, developed whooping cough during the course of inoculations. Fourteen developed whooping cough within 5 to 75 days after completion of inoculations (Table VI). One child escaped the disease. As pertussis appeared in these children, they remained in their original wards and continuously exposed each other and the other children in the wards.

In the interpretation of the course of events in the 16 children whose cases are detailed in Table VI (Cases 1 to 16), the following facts must be borne in mind. The children were all under 16 months of age. Ignoring the days of possible indirect exposure, we know that they were directly exposed for from 34 to 104 days, the total possible exposure varying from 45 to 117 days. Included in this period is a period of exposure for 26 to 28 days before inoculation with formalinized vaccine and a 14-day period of vaccination. After the completion of inoculation the interval for the development of whooping cough was from 5 to 30 days in 8 children, from 40 to 60 days in 7 children, and 75 days in one child who was directly exposed for 104 days.

Why, after a period of apparent immunity, should there be a shift or change in resistance as evidenced by the development of whooping cough? An explanation of this phenomenon is offered by the work of Hektoen and Welker,[15] who state that "in the presence of antibody in the blood, the introduction of the specific antigen may be followed by the reduction to complete disappearance from the blood of the antibody for a time." This is the so-called "negative phase in immunization." Brieger and Ehrlich[16] first observed this phenomenon in their work with tetanus toxin in 1893. Salmonsen and Madsen[17] demonstrated a similar negative phase in the curve of antibody production during progressive immunization. The phenomenon of late infection with pertussis as shown in Table VI may be explained on the basis of the depression of antibody resulting from continued exposure to *Hemophilus pertussis* antigen. It is our thought that continued exposure to large doses of *H. pertussis* may catch these children in a negative phase and result in the development of whooping cough in inoculated and apparently immunized children.

On June 28, 1935, three uninoculated children, directly exposed to the first case for at least twenty-five days, because of severe undiagnosed coughs and suspicious pneumonic findings, were removed from

the fifth floor to the isolation ward on the first floor at St. Vincent's Hospital. Sixty-four children in three other wards on the first floor were thus indirectly exposed by nurses and attendants. On the day following the transfer, a diagnosis of whooping cough was made on these 3, and prophylactic inoculations were immediately started on all the other children on the first floor. Of the 64 indirectly exposed children, 54 received five intracutaneous injections of the formalinized vaccine. The remaining 10 received another form of vaccine and were not included in our series. In this series of 54, the number in each age group was as follows: 34 from 1 to 6 months; 10 from 6 to 12 months; 5 from 12 to 24 months; and 5 from 24 to 36 months (Table VII).

TABLE VII

ANALYSIS OF RELATION OF EXPOSURE TO ONSET OF PERTUSSIS IN 54 FORMALINIZED VACCINATED CHILDREN (FIRST FLOOR, ST. VINCENT'S INFANT AND MATERNITY HOSPITAL)

AGE (MO.)	NUMBER OF CHILDREN	DAYS OF EXPOSURE		TOTAL DAYS' EXPOSURE BEFORE ONSET COUGH	DAYS EXPOSED BEFORE INOCULATION		PERIOD OF INOCULATION (DAYS)	RESULT	
		INDIRECT	DIRECT		DIRECT	INDIRECT		PERTUSSIS	NO PERTUSSIS
	25	56	0	--	0	2	14	2* on 12th	25
Under 6	2	13	2	15	2	0	14	day after ex-	
	7	42	14	56	0	2	14	posure	7
6 to 12	10	56	0	--	0	2	14	0	10
12 to 24	5	56	0	--	0	2	14		5
24 to 36	5	56	0	--	0	2	14		5
Total	54							2	52

*Two infants, 2 months of age, showed pertussis on tenth day after inoculations were begun.

Two infants of this group of 54, aged 2 months, directly exposed for 2 days before receiving the first dose of vaccine, developed whooping cough before the inoculations were completed. During the period preceding diagnosis, they directly exposed, in the same room, 7 infants ranging in age from 2 to 6 months, for a period of fourteen days. After an observation period of thirteen days, the first 2 infants began to cough and were isolated under a tentative diagnosis of whooping cough, which later proved correct. The 7 infants who had been in intimate contact with them did not develop whooping cough. The remaining 45, indirectly exposed, also remained free of whooping cough.

In comparing this series with that of the fifth floor (Table VI), a recognition of two distinct situations must be made. In the fifth floor group, prophylactic inoculation was delayed for twenty-six days during and following which there was constant direct exposure to children

with frank pertussis who remained in the same beds and rooms in which they developed the disease. The contacts were not segregated. In contrast, the first floor group was inoculated 2 days after exposure, and in general there was only indirect exposure since the 5 children with whooping cough were segregated in a room on the same floor a few days after symptoms developed. Early inoculation and less prolonged constant direct exposure to frank pertussis explains the lower incidence of whooping cough in this group.

Between July 1, 1935, and Jan. 10, 1936, during the height of the epidemic, 109 children were admitted to St. Vincent's Infant and Maternity Hospital. They were given their first inoculations of formalinized pertussis vaccine on the day of admission. The succeeding routine four doses were administered during the following fourteen days. None of these children were directly exposed to pertussis. Table VIII is an analysis of results in this group of children. Ten of these developed whooping cough, 99 remained free.

TABLE VIII

RESULT OF IMMEDIATE INOCULATION AND SIMULTANEOUS INDIRECT EXPOSURE IN 109 CHILDREN (ST. VINCENT'S INFANT AND MATERNITY HOSPITAL)

AGE (MO.)	NUMBER OF CHILDREN INOCULATED	DEVELOPED PERTUSSIS		DAYS OF INDIRECT EXPOSURE	DAYS OF EXPOSURE BEFORE ONSET OF COUGH	NO PERTUSSIS
		NO.	AGE			
Under 6		1	2 mo.	37	37	
		1*	3 mo.	23	23	
		1	3 mo.	39	39	
		1	3 mo.	105	105	
Total	46	4				42
6 to 12		1	11 mo.	69	69	
		1	6 mo.	82	82	
		1	6 mo.	160	160	
		1	7 mo.	164	164	
Total	42	4				38
12 to 24		1	17 mo.	48	48	
Total	17	1				16
24 to 36		1	3 yr.	62	62	
Total	4	1				3
Grand Total	109	10				99

*Sudden death on the twenty-first day of whooping cough.

An explanation of what constituted "indirect exposure" in the Institution is necessary. The construction of the hospital affords no quarters or physical facilities for satisfactory isolation. Segregation was possible, but quarantine was impossible. There are two or three intercommunicating rooms with a common bath and supply room to each ward. Resident physicians, nurses, and attendants circulate between infected and noninfected beds, rooms, and wards on all floors in the pursuit of their duties. There were no "clean" wards. As soon

as a room in one of the wards became "clean," the children from the ground or observation floor were, on the completion of their inoculations, removed to these quarters, where indirect exposure became mediate. These children fell within the age group most susceptible to whooping cough. In none of the 109 was there a history of previous pertussis.

At the Children's Department of Cook County Hospital in the ward for open tuberculous patients, a female, 5 months of age, was admitted on June 5, 1935, with a cough of two weeks' duration. Nine days later her twin brother was admitted to the same room. The twins, admitted for tuberculosis, were found to have in addition congenital syphilis and on July 8, a third child, age 2 years, because he also had tuberculosis and syphilis, was placed in the same room. The spasmodic cough of the twins was at first attributed to their tuberculosis, but proved to be pertussis, and thus these three children became the source of indirect exposure for the entire ward. By July 25, the second twin was coughing severely, and the third child in the room had a cough sufficiently characteristic to permit a clinical diagnosis of pertussis.

Twenty of the tuberculous children in this group gave a history of never having had whooping cough. Formalinized pertussis vaccine inoculations were begun in these 20 children on July 30, five days after the diagnosis of whooping cough was made certain, but after fifty-five days of indirect exposure. Seventeen with a previous history of pertussis were not inoculated. Of these, one child, 6 years old, with a history of whooping cough four years previously and poor health thereafter, developed pertussis on September 2, after three months of indirect exposure. None of the 20 children with a negative history of previous pertussis and inoculated with formalinized vaccine developed the disease (Table IX).

TABLE IX

37 CHILDREN WITH ACTIVE TUBERCULOSIS INDIRECTLY EXPOSED TO PERTUSSIS (COOK COUNTY HOSPITAL)

NO HISTORY OF PREVIOUS PERTUSSIS INOCULATION						HISTORY OF PREVIOUS PERTUSSIS NO INOCULATION			
AGE	NUMBER OF CHILDREN	DEVELOPED PERTUSSIS	PERIOD OF INDIRECT EXPOSURE (DAYS)		TOTAL INDIRECT EXPOSURE (MO.)	NUMBER OF CHILDREN	DEVELOPED PERTUSSIS	PERIOD OF INDIRECT EXPOSURE (MO.)	PERIOD OF EXPOSURE BEFORE ONSET OF COUGH
			BEFORE INOCULATION	AFTER INOCULATION					
1 to 2 yr.	3	0	85	80	4½	1	0	4½	------
2 to 3 yr.	3	0	55	80	4½	2	0	4½	------
3 to 13 yr.	14	0	55	80	4½	13		4½	------
							1	3	3 mo.
Total	20	0				16	1		

COMMENT

A formalinized pertussis vaccine with a concentration of 10 billion organisms per cubic centimeter was used to immunize both private patients and children in institutions. The study was made during a period of high incidence of the disease in Chicago, with an epidemic at one institution and a threatened epidemic at a second institution. The importance of the carrier contact in the spread of whooping cough, as in other childhood infectious diseases, cannot be easily measured. In our experience, the "carrier" is as important a factor as the child with the recognized disease.[1] It was not possible to estimate the degree of direct and carrier exposure in any of our groups. Such an analysis would have necessitated the repeated nose and throat culture of all who had contacted the private patients. This is a procedure obviously impossible in a large city, where children congregate in constantly shifting groups in public and church schools, on street cars, and at the movies. In our previous study, *Hemophilus pertussis* was cultured from the nose and throat of children long since recovered from the disease, and occasionally a "contact" child with what seemed to be a "natural immunity" was found to have a postive culture.[1]

An institution such as St. Vincent's Infant and Maternity Hospital, where children remain for as long as four years, and where no whooping cough had existed during the previous two years, afforded an excellent opportunity for observation. There had been no casual visitors in the wards. The first child who contracted the disease had been in the institution during its entire 2½ months of life. There was no movement of infected children between wards on the same floor after this case was diagnosed. Nevertheless, the disease continued to appear in new and distant foci whose only intercommunication was through nurses, residents, and attendants. A similar dissemination has been observed by one of us (M. L. B.) many times at the Cook County Hospital. The second focus of whooping cough on the fifth floor appeared in an isolation ward. Both the first and the second children were crib infants.

Some of our closely observed, room-isolated, vaccinated crib age infants, developed the disease after weeks of exposure. Immunity passed through a negative phase or as von Groehr would phrase it "sensitivity predominated over resistivity." A negative phase occurred late, the delicate balance between infection and immunity was lost, and the disease occurred. This is expected occasionally with whooping cough immunization, and it must be expected with any infectious disease. One cannot expect to produce a 100 per cent result. Even nature does not, as evidenced by the fact that the mother of one of our "failures" gave a clear history of having had whooping cough previously, but nevertheless contracted it the second time from her daughter. Recurrent infections have been observed by us person-

TABLE X

SUMMARY OF RESULTS IN 378 COMPLETELY INOCULATED CHILDREN

PRIVATE PATIENTS				ST. VINCENT'S INFANT AND MATERNITY HOSPITAL				COOK COUNTY HOSPITAL			SUMMARY		
AGE GROUP	TOTAL	NO DISEASE	% NO DISEASE	TOTAL	NO DISEASE	% NO DISEASE	COMPLICATIONS	TOTAL	NO DISEASE	% NO DISEASE	TOTAL INOCULATED	NO DISEASE	% NO DISEASE
Under 6 mo.	0			85	79	93	One, pneumonia; one, sudden death	0			85	79	93
6-12 mo.	96	94	98	62	49	79		0			102	88	86
12-24 mo.	30	25	83	27	21	77		3	3	100	55	48	87
24-36 mo.	21	18	86	9	8	88		3	3	100	32	30	94
Over 3 yr.	100	90	90	0				14	14	100	104	103	99
Total	247	227	92	183	157	86	2	20	20	100	378	349	89

ally in scarlet fever and chicken pox with a much shorter interval of immunity. It is, in our opinion, an error to promise parents 100 per cent protection by natural or artificial immunization.

The reactions to the vaccine were mild with few exceptions. Occasionally children react violently to any foreign protein. A child with far-advanced, long-observed pneumonic tuberculosis died of miliary tuberculosis after inoculation. The other children in the tuberculous ward (many of them of adult type) showed no ill effects. In a previous experience in the same ward using another method of immunization, a larger percentage acquired the disease, and the death rate from pertussis and tuberculous extension was higher. We recognized the undesirability of inoculations in such tuberculous individuals, but as a public health measure, the greatest good to the greatest number must be the guiding principle.

There were fewer and less severe reactions in the intracutaneously injected groups than in those to whom deeper injections were given. It is doubted that the whole dose remains intracutaneous. But through the needle sinus, the infiltration from the superficial tissue continues to act on that great immunizing organ, the skin. Pasteur was the first to demonstrate this principle. Besredka and, lately, Tuft have redemonstrated the value of intracutaneous inoculations.

In evaluating the use of protective measures, one must consider not only morbidity, but complications and mortality as well. The course of the disease in the group which was inoculated and contracted the disease was less severe than in uninoculated children. The group at St. Vincent's Hospital was young. They were at the age when interstitial pneumonitis most commonly occurs. There were no such complications in the completely inoculated group. In the series one sudden death occurred, not explained by autopsy but probably belonging in the group "sudden death during whooping cough." Ninety-two per cent of the children in our private practices have escaped the disease up to this time (Table X). During the epidemic period of study at St. Vincent's Infant and Maternity Hospital, 86 per cent escaped the disease. In the group at the Cook County Hospital 100 per cent remained well.

It was interesting to note that of 109 children who were inoculated and then constantly indirectly exposed (Table VIII), 99 remained free from the disease. It would seem that with the intracutaneous method, a more rapid immunization had been produced than has been thought possible by other observers using the subcutaneous route. It is interesting to note that in the 10 who acquired whooping cough, the period of freedom from disease varied from 37 to 164 days after inoculation. An analysis of the 29 completely inoculated children who developed whooping cough appears in Table XI. Permanent immu-

nity, therefore, is not certain. This is quite in accord with clinical observation of uninoculated children. They may safely pass through several epidemics and finally acquire the disease.

TABLE XI

ANALYSIS OF 29 INOCULATED PATIENTS DEVELOPING PERTUSSIS
(ST. VINCENT'S INFANT AND MATERNITY HOSPITAL)

AGE (MONTHS)	PERTUSSIS PATIENTS	KNOWN PERIODS OF TOTAL EXPOSURE (DAYS)	DAYS ELAPSING FROM COMPLETION OF INOCULATION TO ONSET OF COUGH
Under 6	6	23-37-39-82-103-105	9-23-25-40-60-91
6 to 12	13	45-55-60-65-69-70-82-85 85-85-117-160-164	5-15-20-25-30-45-45-45 55-68-75-146-150
12 to 24	7	48-51-67-69-85-100	11-13-27-29-34-45-60
24 to 36	2	62	48-57
Over 3 yr.	1		240

CONCLUSION

A vaccine modified by formalinization given intracutaneously or subcutaneously in a total dosage of 30 billion organisms has proved an effective measure in the prophylaxis of whooping cough.

Only exposure to another epidemic will demonstrate the length of time protection will endure.

REFERENCES

1. Blatt, M. L., Levin, I. M., Dale, M. L., Mansowitz, D., and Kessler, H.: Am. J. Dis. Child. **46**: 926, 1933.
2. Culotta, C. S., Harvey, D. F., and Gordon, E. F.: J. PEDIAT. **6**: 743, 1935.
3. Sauer, L. W., and Hambrecht, L.: Am. J. Dis. Child. **37**: 732, 1929.
4. Rich, A. R., Long, R. H., Brown, J. H., Bliss, E. H., and Holt, L. E.: Science **76**: 330, 1932.
5. Shibley, G. S.: Proc. Soc. Exper. Biol. & Med. **31**: 576, 1934.
6. MacDonald, H., and MacDonald, G. J.: J. Infect. Dis. **53**: 328, 1933.
7. Besredka, A.: Immunity in Infectious Disease, Baltimore, 1930, Williams & Wilkins Company, pp. 90-91.
8. Kendrick, P.: Am. J. Hyg. **18**: 442, 1933.
9. Tuft, J.: J. Immunol. **21**: 85, 1931.
10. Tuft, J.: J. Lab. & Clin. Med. **16**: 552, 1931.
11. Personal Communication with Dr. H. O. Jones, Chicago Health Department.
12. Knoepfelmacher, W.: Whooping Cough, von Pfaundler and Schlossmann, The Diseases of Children, Philadelphia, 1935, J. B. Lippincott Company, Vol. III, pp. 328-329.
13. Friedlander, A.: Whooping Cough, Abt's Pediatrics, Philadelphia, 1925, Vol. VI, pp. 130, W. B. Saunders Company.
14. Feer, E.: Textbook of Pediatrics, translated by J. P. Sedgwick, C. A. Scherer, Philadelphia, 1922, J. B. Lippincott Company, pp. 673.
15. Hektoen, L., and Welker, W. H.: J. Infect. Dis. **57**: 337, 1935.
16. Brieger and Ehrlich: Ztschr. f. Hyg. u. Infectionskr. **13**: 336, 1892.
17. Salmonsen and Madsen: Ann. Inst. Pasteur **11**: 315, 1897.

185 NORTH WABASH AVENUE

VON GIERKE'S GLYCOGEN STORAGE DISEASE

Case Report With Unusual Findings

Maurice M. Fliess, M.D., Clifton Forge, Va., and
Samuel M. Bloom, M.D., New York, N. Y.

SINCE von Gierke's original report in 1929 on the syndrome that has since borne his name, there have been a number of reports, mostly in the foreign literature, concerning the condition of glycogen storage disease. No attempt will be made in this paper to review the literature, but we will merely list the authors who have reported cases in the American literature. The first case, one of the hepatic type, was reported in April, 1934, by Rauh and Zelson,[1] and another similar case was reported by Wilder[2] in August, 1935. Antopal, Heilbrunn, and Tuchman[3] presented a case of the cardiac type in September, 1934. Humphreys and Kato[4] presented three cases of the cardiac type in September, 1934, these cases having been diagnosed postmortem. Lindsay, Ross, and Wigglesworth[5] reported one case of the hepatic type in September, 1935, as did Hogg and Sidbury[6] in June, 1937. This makes a total of eight cases in the American literature, equally divided into the cardiomegalic and the hepatomegalic types

It is the purpose of this paper to present a fairly typical case of von Gierke's disease of the hepatic type, but also revealing cardiac involvement and several interesting features previously unrecorded in descriptions of this disease.

CASE REPORT

S. T., female infant, aged 2 years and 2 months, was admitted to the hospital April 2, 1937. There were six other children in the family who were all well. The mother was 40 years old and the father 42 years of age. The family history was irrelevant. The mother stated that the baby was pale all her life. She had noticed abdominal enlargement, but she was uncertain as to the time this observation was made. The patient was breast fed for six months and was then given cow's milk, orange juice, and occasionally vegetables. She had never had any cod liver oil or solid foods. Her teeth had developed normally; she sat alone at 9 months and stood with support at 10 months. She has never walked. She spoke single words at 1 year of age. She had no illnesses except pneumonia at the age of 4 months. For the month prior to admission she had taken an iron preparation and had received two intramuscular injections of blood; for two days prior to admission she had cough and fever and was sent to the hospital with a diagnosis of pneumonia.

The physical examination revealed a desperately ill, 26-month-old infant, with extreme pallor and a slightly subicteric tint. The facies was somewhat mongoloid in character. Respirations were very rapid, and there was marked air hunger.

From the Department of Pediatrics, Chesapeake and Ohio Hospital, Clifton Forge, Va.

There were scattered moist râles throughout both lungs but no evidence of pneumonia. The heart was enlarged, and there was a loud systolic murmur heard best at the apex and widely transmitted. The liver was tremendously enlarged, extending to the iliac crest and also firm and smooth. The spleen was not palpable, and there was no adenopathy. The extremities were poorly developed, and the fingers were long and tapering. The patellar reflexes were absent. Blood studies showed an extreme anemia with a hemoglobin of 15 per cent and red blood count of 810,000. An immediate transfusion of 260 c.c. was given by the direct method.

The clinical course during her stay in the hospital is outlined in Table I and only the most important points will be mentioned here. On the day after admission she seemed somewhat better, but considerable abdominal distention had developed. The urine showed considerable acetone and a trace of albumin. The

Fig. 1. Fig. 2.

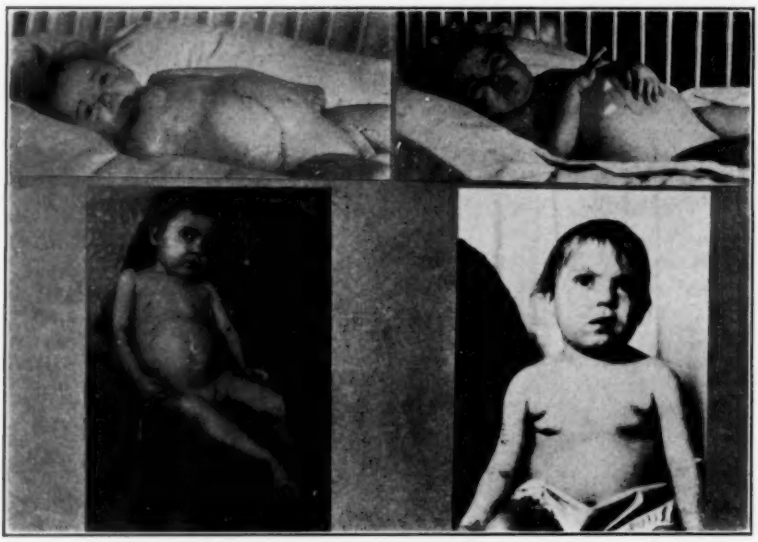

Fig. 3. Fig. 4.

Fig. 1.—Appearance on April 3, 1937. Note extreme pallor and marked hepatomegaly.

Fig. 2.—Appearance on April 6, 1937, at height of edema. Liver smaller. (Upper line is costal margin.)

Fig. 3.—April 16, 1937. Appearance at discharge. Note marked diminution in size of liver.

Fig. 4.—June 26, 1937. Liver not palpable.

icterus index was 12. On this date liver extract was given intramuscularly; this was continued daily, and later on every other day. On the following day, another transfusion of 260 c.c. was given and because of the distention, pitressin was given every four hours for seven doses. Digitalone was also given and continued for four days. The fasting blood sugar on April 4, 1937, was 118. On April 5 she began to develop a nephrotic type of edema which reached its height on the following day. The acetonuria disappeared after three days in the hospital, and on several occasions she had moderate glycosuria. The Mantoux and the Kahn tests were negative. On the day that the edema began cholesterol was 500. The appearance of the patient at the time was typical of that of nephrosis. It is inter-

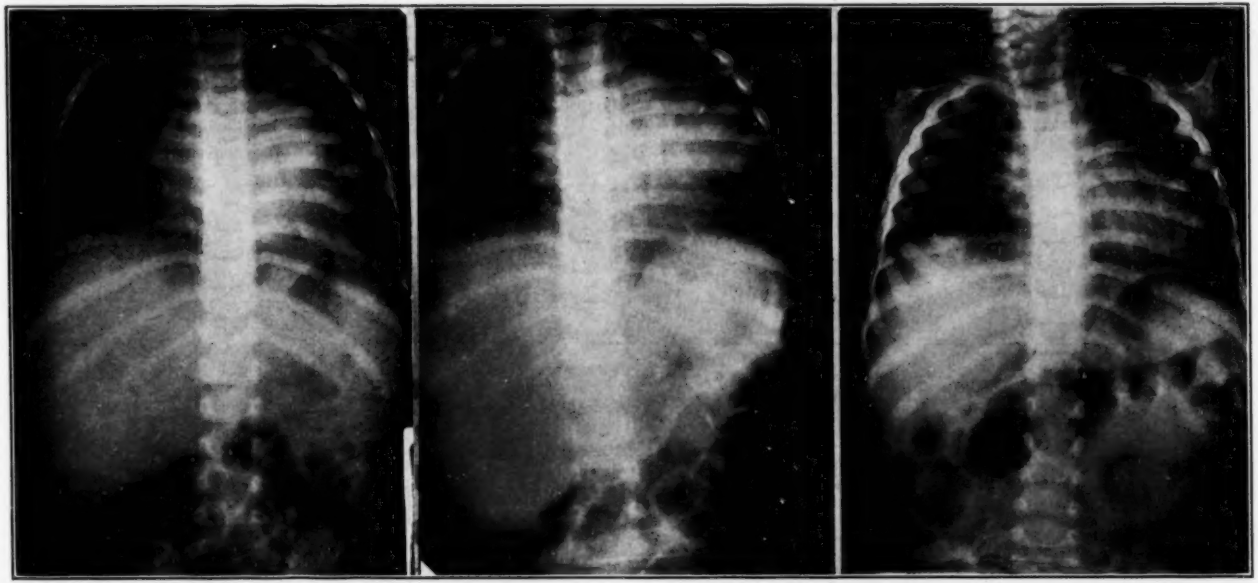

Fig. 5. Fig. 6. Fig. 7.

Fig. 5.—Roentgenogram taken April 3, 1937, showing liver and heart enlarged.
Fig. 6.—Roentgenogram taken April 5, 1937, at the beginning of edema. Liver and heart are more enlarged.
Fig. 7.—Roentgenogram taken June 26, 1937. Liver and heart are practically normal in size.

TABLE

VON GIERKE'S

DATE	4/2/37	4/3/37	4/4/37	4/5/37	4/6/37
TEMP.	101.6-102.2° F.	101.2-103.8° F.	102.6-104.4° F.	100.4-103.8° F.	99.4-102° F.
Clinical Findings	Desperately ill Extreme pallor Subicteric tint Mongoloid facies Marked air hunger Respiration very rapid Scattered moist râles Loud systolic murmur Liver firm and smooth to iliac crest Spleen—not palpable No adenopathy Extremities poorly developed Fingers long and tapering Reflexes absent	Color better Respiration rapid Marked distension Hypostatic râles Measurements Head—18½″ Thorax—19½″ Abdomen—23½″	Marked distention Seems weak	Edema of face, body and extremities Pulse irregular (extrasystoles) Marked distention Moist râles in bases	Marked edema Pulse regular Distention less Liver subsiding Chest almost clear Heart slow and regular—no murmurs Weight, 27 lb. 14 oz.
Laboratory Findings	Hemoglobin—15% R. B. C.—810,000 W. B. C.—16,400 Polys—38% Urine Albumin Acetone Sugar Diastase Urobilin Urobilinogen	 Trace Pos. Neg. Icterus index—12	Hemoglobin—25% R. B. C.—1,410,000 W. B. C.—15,400 Polys—28% Pos. Pos. Blood sugar—118	Hemoglobin—45% R. B. C.—2,190,000 W. B. C.—14,800 Polys—35% Heavy Trace Pos. Pos. More than 80 units Cholesterol—500 Mantoux—Neg. Kahn—Neg.	Hemoglobin—55% R. B. C.—3,070,000 W. B. C.—18,300 Polys—55% Heavy Trace Neg. Neg. X-ray Pituitary—normal Long bones—normal
Treatment	Transfusion—260 c.c.	Liver extract 1 c.c. intramuscularly	Transfusion—260 c.c. Liver extract—1 c.c. intramuscularly Pitressin 3 min. q. 4 h. (2 times) Digitalone (½) q. 4 h.	Liver extract 1 c.c. intramuscularly Pitressin 3 min. q. 4 h. (5 times) Digitalone (½) q. 4 h. 250 c.c. 20% glucose intravenously	Liver extract 1 c.c. intramuscularly Digitalone q. 4 h.

I

DISEASE

4/7/37	4/8/37	4/10/37	4/12/37	4/16/37	6/26/37
99.8-101.6° F.	NORMAL				
Edema less Respiration—normal Liver decreasing Blood pressure 120/80	Edema clearing Color good Liver smaller, 3 finger-breadths below costal margin	No edema L. B. D. 3 cm. outside nipple Reflexes active		Unsmiling and placid Abdomen—19½″ Length—32½″ Heart moderately enlarged P_2 A_2 Slight systolic blow Liver—2 finger-breadths below costal margin	Talks and laughs Stands with support Liver and spleen not palpable Heart very slightly enlarged No murmur
Weight, 27 lb. 14 oz.	Weight, 26 lb. 6 oz.	Weight, 23 lb. 7 oz.	Weight, 23 lb. 8 oz.	Weight, 21 lb. 11 oz.	Weight, 26 lb.
			Hemoglobin—60% R. B. C.—3,310,000 W. B. C.—7,400 Polys—28%	Hemoglobin—70% R. B. C.—3,450,000 W. B. C.—8,300 Polys—27%	Hemoglobin—80% R. B. C.—4,140,000 W. B. C.—6,400 Polys—40%
Trace Neg. Neg. 40 units	Trace Neg. Neg.	Neg. Neg. Neg.	13 units		
			Cholesterol—286 Urea—15 Blood Sugar Fasting—80 30 min. after 3 min. adrenalin—89	Glucose tolerance Fasting—80 1 hr.—125 2 hr.—100 Gastric analysis Free—0 Combined—63	Blood sugar Fasting—111 45 min. after 5 min. adrenalin—133
Liver extract 1 c.c. intramuscularly Digitalone q. 8 h. Soft diet	Liver extract 1 c.c. intramuscularly Antianemic iron medication p. o.	Liver extract 1 c.c. every other day Continued Antianemic diet			

esting to note that when the edema was at its height the liver was diminishing in size. The edema lasted for five days, and the liver steadily decreased in size; the blood picture became steadily better. There was a weight loss of about 6 lb. during the loss of edema. The condition of the heart improved steadily although a moderate enlargement persisted during the hospital stay. There was an irregular febrile course for six days after which time she was afebrile. The urinary amylase decreased steadily from a reading of more than 80 to 13 units. After the disappearance of edema the cholesterol was 286, the blood urea was normal, and there was no urobilin or urobilinogen in the urine. The glucose tolerance test showed a fasting blood sugar of 80; one hour after the injection of glucose it was 125; two hours after, it was 100 mg. per 100 c.c., showing a subnormal rise and a level that had not reached the fasting level at the end of two hours. Thirty minutes after the injection of 3 min. adrenalin, the blood sugar had risen only 9 mg., which is considerably below normal. At the time of discharge from the hospital, April 16, 1937, the child was much improved and the liver extended only two finger-breadths below the costal margin. The abdomen had decreased 4 inches in size; the heart was moderately enlarged. She was still unsmiling, very placid, and unresponsive. She was last seen June 26, 1937, more than two months after discharge from hospital and her condition was remarkably improved. She talked quite well and responded to stimuli. She was able to stand with support but still was unable to walk. Liver and spleen were not palpable and the heart was only slightly enlarged. She had gained over 4 lb. in weight, and her blood counts were normal. The rise in blood sugar at the time was 22 mg. 45 minutes after the injections of 5 min. adrenalin.

SUMMARY

1. A rather typical case of von Gierke's disease is reported, the ninth in the American literature.

2. The extreme anemia that occurred in this patient has not been mentioned in previous discussions of this disease. The very poor feeding habits in this patient could readily account for the blood picture.

3. A typical but transient nephrotic edema with marked albuminuria occurred; elevation in cholesterol also developed during the course of the disease.

4. The very rapid apparent cure is also extremely unusual, and we are unable to account for this. We are unable to state whether the liver extract or the pitressin had any effect in the rapid recovery.

5. No effort is made to discuss the cause of this syndrome, but it seems from this case that it is certainly a condition not limited to disturbance in the glycogen-glucose metabolism but that also the fat metabolism and other unknown factors are probably involved.

REFERENCES

1. Rauh, L., and Zelson, C.: Am. J. Dis. Child. **47**: 808, 1934.
2. Wilder, Robt. L.: J. PEDIAT. **7**: 214, 1935.
3. Antopal, W., Heilbrunn, J., and Tuchman, L.: Am. J. M. Sc. **188**: 354, 1935.
4. Humphreys, E. M., and Kato, K.: Am. J. Path. **10**: 589, 1934.
5. Lindsay, L. M., Ross, A., and Wigglesworth, F. W.: Ann. Int. Med. **9**: 274, 1935.
6. Hogg, P., and Sidbury, J. B.: J. PEDIAT. **10**: 798, 1937.

VARICELLA COMPLICATED WITH ACUTE THROMBOCYTOPENIC PURPURA AND GANGRENE

ALBERT V. STOESSER, M.D., AND WILLIAM W. LOCKWOOD, M.D.
MINNEAPOLIS, MINN.

ACUTE thrombocytopenic purpura with gangrene occurs with sufficient rarity as a complication of varicella to make this report of one case of interest. It is well known that purpuric manifestations may occur during the convalescent period of any one of the exanthems, but the association of purpura with varicella is most uncommon. Tancredi[1] observed two cases in 1933, and Cohen[2] had one case which he reported in 1936. His patient was a boy 6½ years old who, on the seventh day after the onset of a typical attack of varicella, developed bleeding from the mouth and very many ecchymotic areas over his entire body, especially under the chin and on the arms and ankles. Wherever the boy scratched, new spots would appear. The platelet count was decreased, but in a few weeks it returned to the normal level and bleeding stopped.

Gangrene or extensive necrosis of the skin and underlying tissues at and around the site of the large pocks occurs occasionally as a serious complication of varicella. A review of the literature appears with the report of a fatal case of bullous and gangrenous varicella by Gordon[3] in 1927. Schamberg and Kolmer[4] also list numerous references to this complication of chicken pox and consider it an infection most common in debilitated infants or small children, more especially those in whom the varicella is preceded by some other illness. Barenberg and Lewis[5] had an opportunity to follow the course of 2,000 cases of varicella and observed only one case of gangrenous varicella. This was in a female child 21 months old. She was well nourished and free of any other diseases. Recently Wishik and Bullowa[6] have made a study of 2,534 patients with varicella admitted to the Willard Parker Hospital of New York during a five-year period. Cutaneous gangrene occurred in only four patients. In all of these cases the gangrene developed during the first week of the chicken pox, and it was preceded in three patients by cellulitis. In the fourth case, a 3-year-old boy with mild varicella, the fingers of the left hand displayed a purplish discoloration, and the next day there was a similar involvement of the right foot and lower part of the leg. A few days later dry black gangrenous patches appeared. They involved all the fingers and most of the left hand, the dorsum of the right foot, the

From the Pediatric Division at the Minneapolis General Hospital, the Department of Pediatrics of the University of Minnesota.

lower third of the anterior surface of the right leg, and an area below the left knee. Then demarcation set in and within a few days the two distal phalanges of each finger and of one toe, and the skin of the leg and foot separated.

Hoyne[7] who has made extensive observations in Chicago reports a similar case. He states that his case was that of a girl 8 years old who had only a moderate number of lesions on the body. However, a marked ecchymosis and edema of the entire left thigh appeared. The right leg below the knee also was swollen and tense. The patient died before gangrene set in. At autopsy a large retroperitoneal hemorrhage was found as well as hemorrhages into the muscles and overlying tissues. Hoyne feels that varicella in which there is a hemorrhagic diathesis is perhaps the most unusual of all forms. The development of extensive gangrene with the loss of part of an extremity or extremities and recovery of the patient makes the complication still more rare. For this reason we present the following case:

D. R., a boy, aged 3 years and 10 months, was admitted to the Minneapolis General Hospital on Nov. 13, 1936, for a thorough study in order to determine the cause of a precocious physical and genital development. The child was born at full term by normal delivery. Growth was rapid during infancy and at the age of 5 months the child could walk, and at the age of 8 months he was able to push his crib across the room. He was advanced mentally, for at the age of 3 years he could run errands to the store and make change with some degree of accuracy. He had a vivacious personality being unrestrained in speech, friendly, boisterous, and speaking in a deep voice which was quite plain. There was no history of any diseases. The family history was essentially negative. There were no brothers and sisters, and the father and mother were in good health. The Wassermann and tuberculin tests were negative.

Physical examination revealed a fairly well-nourished white boy 3 years and 10 months of age. His stature was that of a child of about 8 years, for his weight was 54 pounds and his height 47 inches. His body was well proportioned, being quite muscular. No axillary hair could be found, and pubic hair was sparse. The genitals were the size of those of a boy at puberty. Palpation of the testes yielded no tumor nodule, and likewise abdominal palpation revealed no mass in the adrenal regions.

The fundi showed no evidence of increased intracranial pressure. Roentgenograms of the skull gave no indication of erosion of the sella. The roentgenogram study of the wrists revealed a developmental picture or ossification of a normal 8-year-old child. Pyelography showed no distortion or displacement of the kidney. Encephalography was planned, but at this time the child developed chicken pox and was discharged from the hospital on Dec. 7, 1936.

Five days after the appearance of varicella the mother observed large bluish discolorations on the thighs of her son. They were considered by the parents to be bruises since the child had been up and very active at home. There were very few pocks and no fever. During the next few days, the areas of ecchymosis began to get deeper in color and spread. Then suddenly the child became listless. He was admitted at once to the hospital Dec. 15, 1936, the eighth day after the onset of his illness.

The general appearance of the child was about the same as on the first admission except that he was very quiet and his color was poor. His temperature was sub-

normal. On the cheeks and over the upper part of the trunk there were a few pocks which had dried and were covered by hard brown scabs. The legs showed marked changes. They were edematous and over the outer aspect of both thighs, the right leg from knee to ankle and both feet there were large ecchymotic areas. The pocks on the legs were surrounded by small hemorrhages and some of those located in the discolored areas were replaced by bullae varying in size from 0.5 to 6 cm. in diameter (Fig. 1). These blebs easily ruptured yielding a bloody serous fluid and exposing an inflamed area beneath.

Fig. 1.

Fig. 2.

Fig. 1.—The extensive purpura of both lower extremities is illustrated. Note the bullae over the areas of ecchymosis.

Fig. 2.—Gangrene has caused the skin and subcutaneous tissue to slough away exposing the muscles and tendons.

The hemoglobin was 72 per cent with 26,050 white blood cells and a differential count of 87 per cent polymorphonuclear cells, 6 per cent lymphocytes, 4 per cent monocytes, and 3 per cent eosinophiles. The platelet count was 40,000, the bleeding time was over 25 minutes, and the coagulation time 10 minutes. The blood culture was negative. The patient was given a transfusion of 250 c.c. of citrated blood. In spite of this procedure the legs became more swollen, the edema spreading upward over Poupart's ligament to the lower abdomen and also to the scrotum. The boy

appeared to be in shock, his face being very pale and the skin of the upper extremities and upper trunk cold and moist. The hemoglobin continued to drop to 43 per cent with the white cell count rising to 42,000. A second transfusion of 350 c.c. of citrated blood was performed. The general condition of the patient improved, but the following day the legs and feet were cold, and the dorsalis pedis pulse was very weak. The areas of ecchymosis were less blue in color, but the legs were tense and glistening. Another transfusion of 350 c.c. of blood was given and at the same time 0.5 c.c. of moccasin venom was injected intramuscularly. The venom therapy was repeated on each of the following two days, the dose being increased to 1 c.c. The platelet count rose to 150,000, but the hemoglobin continued to fall until it reached 30 per cent on the ninth hospital day. The edema of the abdomen and scrotum began to disappear.

Fig. 3.

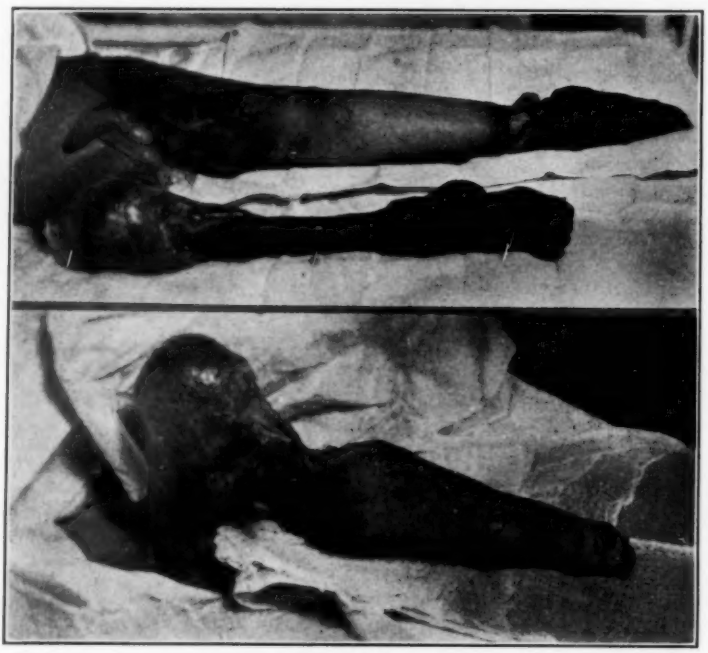

Fig. 4.

Fig. 3.—The gangrene has involved the muscles, and lines of demarcation have appeared.

Fig. 4.—The infected amputation stumps are shown.

Necrotic inflammation now appeared at the site of the bullae in the discolored areas. It spread rapidly and involved the skin and subcutaneous tissue, exposing the muscles and tendons (Fig. 2). Four transfusions were given on alternate days —a total of 1,500 c.c. of blood. The hemoglobin rose to 75 per cent, and the white cell count fell to 12,000. The platelets were at 190,000 while the bleeding time was 7 minutes and 35 seconds. The gangrene was not controlled, and the exposed muscles became dry. Both feet underwent dry gangrene (Fig. 3). A definite line of demarcation appeared below the knee on the right leg and at the ankle of the left leg on the fifteenth hospital day. At no time did the patient complain of any pain in the lower extremities.

Coincident with the gangrenous condition of the legs, small areas of necrosis developed at the site of one chicken pox lesion on the left cheek and another on the right shoulder. These lesions began to heal in one week, but the legs did not improve, and on the twenty-third hospital day the right leg and the left foot were removed with little difficulty, the dry gangrene having progressed almost to the point of complete spontaneous amputation. The stumps became infected, but following constant local treatment and two more transfusions totaling 700 c.c., slow and satisfactory healing began to take place (Fig. 4).

One month later ecchymotic areas appeared over the gluteal regions. The patient had some fever due probably to the small amount of infection which was still present in the amputation stumps and in the granulation tissue covering the muscles of the lateral aspect of the left thigh. Although the hemoglobin was 90 per cent, the platelet count had fallen to 130,000. Several transfusions were immediately given and the platelet count rose to 200,000. The purpura disappeared only to reoccur a few more times, and in each instance a transfusion appeared to be necessary to control the ecchymoses. On April 20, 1937, a little over four months after admission to the hospital, the purpura finally disappeared. Following this, the patient improved rapidly. His wounds healed nicely, although a few operations involving trimming of the stumps and skin grafting were necessary (Fig. 5). The hemoglobin remained between 80 and 90 per cent and the platelet count around 300,000. The boy was discharged approximately one year after admission to the hospital although he was not quite ready for artificial limbs. During his stay in the hospital he had received seventeen transfusions, totaling 5,000 c.c. of blood.

Fig. 5.—The stumps after trimming and skin grafting are healing rapidly. Note also the large area on the left thigh which has filled in with healthy granulation tissue.

DISCUSSION

Purpura is a condition which may be due to any one of several etiological factors. The symptoms may be observed in connection with acute infections, poisonings, metabolic or endocrine disorders, nutritional disturbances, and allergic diseases. This varied association has led to many classifications. The one, however, most commonly used is based on the platelet count—on the presence or absence of thrombocytopenia. With the drop in the platelet count, there is a prolonged bleeding time and a normal clotting time. Thrombocytopenic purpura

may be divided into the essential or idiopathic, and the symptomatic which is secondary to some known etiological factor or factors. Our case belongs to the latter group.

Many observers believe that the majority of the patients developing purpura following acute infections such as tonsillitis, otitis media, scarlet fever, and measles do not have marked changes in the platelet count. The child is usually very ill with a high fever for a short period of time, and then the purpura appears. It may be quite extensive but in spite of this there may be no thrombocytopenia. Our patient, on the other hand, was not very sick during the early stages of the varicella, and his temperature was normal at the time the purpura first made its appearance. The onset was sudden, and it was followed by a rapid extension of the subcutaneous extravasation of blood. The platelet count dropped to a low level.

Fortunately after three large blood transfusions and the administration of three doses of snake venom as recommended by Peck and Rosenthal,[8] the bleeding stopped. Whether the transfused blood or the snake venom was alone responsible for the favorable results could not be determined at that time. Later, however, the patient again developed a series of attacks of purpura over the buttocks, and there was now definite evidence that each attack of ecchymosis was controlled by a blood transfusion. Not until the platelet count was finally raised to, and maintained at, a level of 300,000 did the purpura fail to reappear.

The necrosis or gangrene of varicella has always been a serious complication. Malnutrition, syphilis, or tuberculosis have been considered predisposing causes. Our patient, however, was in the state of good nutrition and his Wassermann and tuberculin tests were negative. The edema of the wall of the lower abdomen and the scrotum suggested a large retroperitoneal hemorrhage similar to the one found in Hoyne's patient. This hemorrhage might have exerted pressure on the large vessels in the lower abdominal cavity and thus caused swelling and gangrene of the legs. A thorough examination of the abdomen including a roentgenogram study failed to give any definite evidence of this internal hemorrhage.

More important was the concomitant appearance of necrotic inflammation at the site of one pock on the face and another on the shoulder. The presence of these areas of gangrene indicated that a probable individual susceptibility to the virus of varicella existed. When the idiosynerasy appeared, the lower extremities were covered with large areas of ecchymosis. They were also edematous probably because of pressure on the blood vessels from deep-seated hemorrhages. The decreased resistance of the tissues under these circumstances may have aided the virus in producing an extensive necrosis or gangrene in this part of the body.

SUMMARY

A case of varicella complicated with acute thrombocytopenic purpura and gangrene is presented. This is a very rare combination.

The lower extremities were chiefly involved. Blood transfusions controlled the purpura, but the necrotic inflammation or gangrene spread quite extensively before it stopped spontaneously. Amputation of a portion of each leg was necessary.

This complication involving blood and vascular changes and destruction of tissue may be due to a marked individual sensitivity to the virus of varicella.

REFERENCES

1. Tancredi, A.: Pediatria prat. **10**: 221, 1933.
2. Cohen, Harry J.: Arch. Pediat. **53**: 773, 1936.
3. Gordon, E.: Arch. Pediat. **44**: 337, 1927.
4. Schamberg, J. F., and Kolmer, J. A.: Acute Infectious Diseases, Philadelphia, 1928, Lea & Febiger, p. 319.
5. Barenberg, L. H., and Lewis, J. M.: Arch. Pediat. **44**: 653, 1927.
6. Wishik, S. M., and Bullowa, J. G. M.: Am. J. Dis. Child. **49**: 927, 1935.
7. Hoyne, A. L.: Practice of Pediatrics by Various Authors, Edited by Joseph Brennemann, Hagerstown, Md., 1937, W. F. Prior Company, Inc., Vol. 2, Chap. 3.
8. Peck, S. M., and Rosenthal, N.: J. A. M. A. **104**: 1066, 1935.

INFLUENCE OF FACTORS BEFORE AND AT TIME OF DELIVERY ON PREMATURE MORTALITY

B. B. Breese, Jr., M.D.
Rochester, N. Y.

IT IS a well recognized fact that further reduction in the infant mortality rate must, in many cities, depend on a reduction in the number of deaths occurring in premature infants. In Rochester, N. Y., the infant mortality rate has been 52 per 1,000 live births over the ten-year period of 1927-1936, inclusive. Deaths from prematurity have represented 18 per 1,000 live births or 34.7 per cent of the total infant mortality rate. This relatively high percentage of deaths from prematurity has, in some communities, especially in Chicago, led to strenuous efforts by the Board of Health working in cooperation with the practicing physicians to lower the deaths among this group of infants. The Chicago Premature Program, which has had the assistance of pediatricians such as Hess,[1] is being watched closely by those interested in the problem. There the effort is being made to bring the care of premature infants in a whole community up to the highest plane available in the most advanced centers.

Another angle of the problem has been stressed by Clifford[2-5] writing from the Boston Lying-In Hospital. At this institution it was felt that further reduction in mortality would have to be accompanied by an improvement in the obstetric handling of premature labors. In order to discover where improvement could be made, a statistical study of 925 premature infants was prepared, and conclusions were drawn about factors in the mother at the time of delivery which were favorable or unfavorable to the infant.

At the time of Clifford's publications we were interested in the premature problem in Rochester, and much of what follows is an outgrowth of Clifford's work.

This present study is an analysis of 987 premature infant records taken from the Rochester Municipal, Strong Memorial, and Rochester General Hospitals, with particular reference to the effects on mortality of conditions in the mother and factors at the time of delivery which might conceivably influence the mortality of the infants.

In this study a premature infant is defined as an infant who weighs less than 2,500 gm. at birth. Only infants born alive and in the three hospitals mentioned are included in the study. By "live" is meant

From the Department of Pediatrics, University of Rochester School of Medicine and Dentistry, and the Strong Memorial and Rochester Municipal Hospitals, and the Rochester General Hospital.

any child with a gestation period of over five months who shows any sign of either cardiac, respiratory, or muscular activity. Obviously many of these infants died very shortly after birth and might, if a less strict definition were used, be considered as stillborn infants. Clifford used five pounds (2,270 gm.) as the dividing line between the full-term and the premature infant.

In common with all other studies, it was found in this survey that the size of the infants at birth was the most important factor influencing mortality. The period of gestation might be used but, since the correlation between these two is high (0.76 ± 0.015) in our series and weight can be more easily obtained than any other measurement, weight has been the criterion of size.

Many studies have divided premature infants into four groups according to weight as follows:

Under 1000 gm.
1000 to 1499 gm.
1500 to 1999 gm.
2000 to 2499 gm.

However, in dealing with premature infants, it seemed that these weight groups might cover too large a range and variations in weight influencing mortality within these groups might be overlooked. Furthermore, it is good statistical practice to have five or more classes in any analysis.

The infants were accordingly divided into seven weight groups as follows:

	NO. CASES	PER CENT OF SAMPLE
Under 1000 gm.	76	7.7
1000-1249 gm.	44	4.5
1250-1499 gm.	68	6.9
1500-1749 gm.	97	9.8
1750-1999 gm.	134	13.6
2000-2249 gm.	184	18.6
2250-2499 gm.	384	39.0
	987	100.1

RELATION OF MORTALITY TO WEIGHT

In Table I is tabulated the relation of mortality to weight with the infants divided into the above weight classes. They are further divided into the series obtained from the Strong Memorial and Municipal Hospitals on one hand and the General Hospital on the other. It will be observed that the difference in mortality between infants of different weight classes is generally statistically significant.

If these results are graphed with weight as the abscissa and mortality percentage as the ordinate, we find that the curves for the General Hospital and Strong Memorial and Municipal Hospitals closely

TABLE I

RELATION OF WEIGHT TO MORTALITY

	UNDER 1000 GM.		1000-1249 GM.		1250-1499 GM.		1500-1749 GM.		1750-1999 GM.		2000-2249 GM.		2250-2499 GM.		TOTAL			AV. WT.	% MORT.	EXP. % MORT.
	L.	D.	L.	D.	L.	D.	L.	D.	L.	D.	L.	D.	L.	D.	L.	D.	T.			
Strong Memorial and Municipal Hosp.	0	38	1	19	11	18	22	19	43	15	64	13	131	6	272	128	400	1885	32	31
% Mortality	100		95.3		62.2		46.4		25.8		16.7		4.4			32				
Rochester General Hosp.	0	38	3	21	14	25	36	20	54	22	97	10	227	20	431	156	587	1970	27	26
% Mortality	100		88.0		64.0		35.8		29.0		9.3		8.1			26.8				
Total	0	76	4	40	25	43	58	39	97	37	161	23	358	26	703	284	987	1935	28	29
% Mortality	100		91.0		63.2		40.3		27.6		12.5		6.8			29.0				
Probable error of % mortality			±2.81		±3.98		±3.32		±2.59		±1.69		±1.07							
Difference of mortality			9.0		27.8		22.9		12.7		15.1		5.7							
Probable error mort. diff.			±2.10		±4.5		±5.1		±4.2		±3.1		±2.0							

approximate each other (Chart 1.) They are combined in Chart 2 which is smoothed and gives a curve slightly convex downward in its middle portion, becoming asymptotic at the ends.

Chart 1.—Relation of weight to mortality in premature infants.
Strong Memorial and Municipal Hospital series ----------
Rochester General Hospital series ——————.

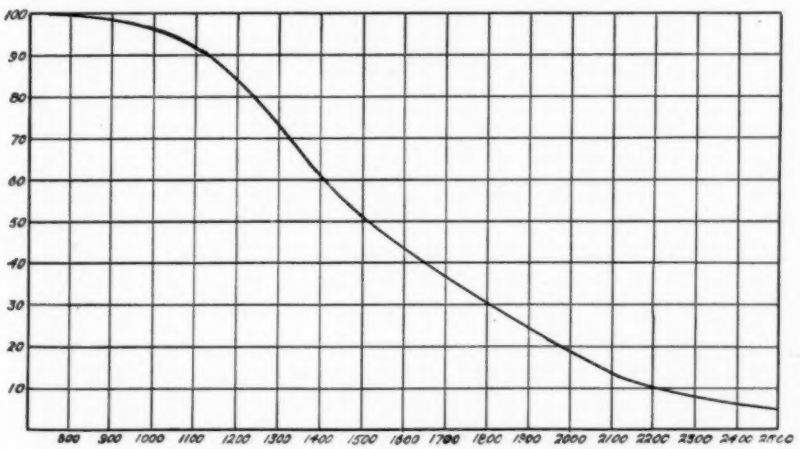

Chart 2.—Relation of weight to mortality—combined series.

Now, because of the very marked correlation between weight and mortality, the effect of other factors influencing mortality is likely to be obscured unless we have some method of correcting mortality figures so that the influence of weight can be eliminated from the comparisons. This is an extremely important point, one which is often

overlooked. Any study of factors influencing mortality which fails to correct for weight will be valueless. Thus, if we are studying the effect of breech delivery as compared with vertex delivery and we find that the mortality of breech deliveries is greater than that of premature infants delivered by vertex, we might conclude that the breech delivery is more deleterious to the infant than vertex delivery. We are not justified in drawing such a conclusion, however, until we have corrected for weight, because it might very well be that the babies delivered with breech presentation are much smaller than those delivered with vertex presentation, and that the difference in mortality is due to the difference in weight and not to the difference in presentation.

Since we are, in this paper, very largely concerned with evaluating effects other than weight on mortality and since infants treated in one way rarely have the same weight distribution as those treated in another way, some method of evaluating the effect of weight on both groups must be obtained.

The obvious method of doing this is to study infants of approximately the same weight, i.e., in the same weight class. This is a perfectly valid way of controlling weight, but certain precautions must be taken. If the weight classes cover too large a range, variations within these weight classes may be great enough so that true control does not exist. Thus, if we compare the mortality of factors A and B in a weight class whose limits vary by 1,000 gm. (for example, between 1,000 and 2,000 gm.), it is perfectly possible to have one group average 1,400 gm. and the other 1,600 gm., which would immediately destroy the weight control. The larger the range of the classes studied, the more readily can this error be made. It is quite obvious in dealing with records of premature deliveries that chance alone does not determine the weight distribution—for example, premature infants who were delivered by forceps are larger than those delivered by breech—and if we are attempting to show that forceps delivery is safer than breech delivery, we must be sure that the reason for this difference is not due to the fact that the infants of breech presentations are on the average smaller and, consequently, have less chance of survival. Because of the tendency, in many of the factors studied, to include infants who are larger or smaller than those representing another factor being compared, we have felt that weight classes of 500 gm. are too large and have used weight classes with a range of 250 gm. But here we find ourselves in the position of having too few cases in each class to have any significance statistically. For this reason we have used a different method of appraising the influence of weight in any factor studied.

Using the mortality in each weight class of the entire group as the base line, we obtained the expected mortality for each factor as follows: The number of cases in each weight class is multiplied by the mortality for that weight group; the sum of all these is then divided by the total number of cases studied. This will give the expected mortality percentage. This can then be compared with the actual mortality and the difference between the two noted.

For example, let us find the expected mortality for premature infants born of mothers with preeclamptic toxemia.

	PER CENT MORTALITY OF 987 CASES		TOXEMIA NO. CASES		
Under 1000 gm.	100.0	×	2	=	200
1000-1249 gm.	91.0	×	4	=	364
1250-1499 gm.	63.2	×	11	=	695
1500-1749 gm.	40.3	×	24	=	970
1750-1999 gm.	27.6	×	33	=	910
2000-2249 gm.	12.5	×	26	=	326
2250-2499 gm.	6.8	×	46	=	313
			146		3778 ÷ 146 = 26 per cent expected mortality

In our series there were 146 infants delivered whose mothers had preeclamptic toxemia. Thirty-nine of the infants died, giving a mortality of 27 per cent. This we call the true mortality, and we find in this particular case that preeclamptic toxemia of itself exerted no demonstrable effect on the premature infant who was born alive.

In Table II are tabulated certain conditions in the mother which are associated with pregnancy and which might influence the life of the premature infant. It must be kept in mind that these infants were born alive, and consequently these figures represent only the residual effect of the condition of the mother on the child after birth. It is perfectly possible that a condition might kill the fetus in utero (such as severe toxemia) and yet have no effect on the child if he were born alive.

In general, it will be noted that the difference in mortality of premature infants born of mothers with different types of conditions is quite marked but that this difference is almost entirely due to the difference in weight of these infants. This can be clearly seen when we compare the expected and true mortality. In most instances they are almost identical.

There is one marked exception to this—hydramnios in the mother. In all of the eighteen cases in which the child was born alive, he succumbed, often as a result of congenital abnormalities. On a basis of weight we should expect 60 per cent of these children to die. The dif-

TABLE II

	UNDER 1000 GM.		1000-1249 GM.		1250-1499 GM.		1500-1749 GM.		1750-1999 GM.		2000-2249 GM.		2250-2500 GM.		TOTAL		TOTAL	AV. WT. GM.	% MORTALITY	EXPECTED % MORTALITY
	L.	D.	L.	D.	L.	D.	L.	D.	L.	D.	L.	D.	L.	D.	L.	D.				
No cause and term	0	22	1	11	7	9	14	14	30	11	73	9	207	16	332	92	424	2065	22	21
Premature rupture of membranes	0	13	0	5	4	9	8	4	8	7	15	1	27	0	62	39	101	1770	39	40
Multiple pregnancy	0	16	1	9	5	11	7	3	20	0	29	6	51	2	113	47	160	1875	29	33
Preeclamptic toxemia	0	2	0	4	5	6	17	7	25	8	23	3	37	9	107	39	146	1362	27	26
Nephritic toxemia	0	4	1	0	1	0	3	4	7	1	3	1	2	0	17	10	27	1672	37	40
Threatened abortion	0	6	0	1	0	1	0	0	0	1	1	0	2	0	3	9	12	1313	75	67
Bleeding	0	7	0	1	1	3	0	0	1	1	2	1	3	0	7	13	20	1450	65	63
Placenta previa	0	1	0	3	0	5	4	2	3	4	7	1	7	2	21	18	39	1850	46	35
Premature separation of placenta	0	2	1	0	0	1	3	2	2	0	1	1	3	0	10	6	16	1702	37	41
Syphilis	0	1	0	0	1	0	0	0	0	0	3	1	9	2	13	4	17	2155	24	17
Pneumonia	0	0	0	2	0	0	0	2	2	0	2	0	0	0	4	4	8	1687	50	43
Pyelitis	0	1	0	3	0	0	1	1	0	0	3	0	3	0	7	5	12	1730	42	42
Cardiac	0	2	1	0	0	1	1	0	0	0	2	0	2	1	6	4	10	1700	40	43
Tuberculosis	0	0	0	0	1	0	0	0	1	0	1	0	1	0	4	0	4	1937	0	29
Hydramnios	0	7	0	2	0	1	0	0	0	3	0	3	0	2	0	18	18	1417	100	60
Other	0	3	1	2	0	1	3	8	3	1	5	0	11	0	23	15	38	1845	39	35

ference of 40 per cent between the true and expected mortality is significant even in this small number of cases.

In placenta previa, the child seems to have slightly less chance of survival than one would expect on the basis of weight. This difference of 10 per cent, however, is too small a difference to be significant from a statistical standpoint and may be due entirely to chance sampling. All we may say is that there is a suggestive difference between the two. Syphilis shows little adverse effect, probably because of treatment of the mother.

On the other hand, multiple pregnancy, and nephritic toxemia in the mother lead to a little better chance of survival than one should expect on the basis of weight. The difference is slight and cannot be proved statistically.

From this study we are forced to the conclusion that various conditions in the mother, associated with the delivery of premature infants, affect the mortality rates of premature infants chiefly inasmuch as they tend to affect the weight of the child. The one definite exception to this seems to be hydramnios. In our series other conditions did not exert enough effect to be significant statistically.

AGE OF MOTHER

If we consider the age of the mother and the effect on the premature child, we find that there is relatively little effect on the mortality of the infant except in the group of women over forty years old (Table III). These women give birth to a group of premature infants whose mortality rate is almost twice as much as that of any other age group. We also find that these women have, on the average, smaller premature infants than those of other age groups. When correction is made for size, the difference between the true and expected mortality is only 11 per cent. If we assume no error for the expected mortality calculation, this difference is not statistically significant, but merely suggestive.

When the number of previous pregnancies in the mother are tabulated with respect to mortality (Table IV), we find that the women who are having their first infants have the best chance of having a live premature infant. This difference, however, is nearly entirely dependent on the fact that they have larger premature infants than multiparous women.

This does not mean that primiparae have larger infants than multiparae, but merely that their children who weigh at birth under 2,500 gm. are larger on the average than those of multiparae. Actually, multiparous women have larger infants at birth, but not larger premature infants when we define prematurity by weight.

TABLE III

RELATION OF AGE OF MOTHER TO MORTALITY

AGE OF MOTHER (YR.)	UNDER 1000 GM.		1000-1249 GM.		1250-1499 GM.		1500-1749 GM.		1750-1999 GM.		2000-2249 GM.		2250-2500 GM.		TOTAL		TOTAL	AV. WT.	% MORTALITY	EXPECTED % MORTALITY
	L.	D.	L.	D.	L.	D.	L.	D.	L.	D.	L.	D.	L.	D.	L.	D.				
15-19	0	9	0	6	4	3	6	5	9	3	17	3	48	3	84	32	116	1957	28	28
20-24	0	19	1	8	5	11	15	10	34	14	59	9	108	6	222	77	299	1987	26	26
25-29	0	17	0	8	9	10	12	9	23	7	35	1	83	8	162	60	222	1940	27	29
30-34	0	18	1	8	3	6	6	9	20	3	24	4	62	3	116	51	167	1887	31	31
35-39	0	6	2	4	2	6	17	4	9	6	21	6	37	2	88	34	122	1922	28	29
40-44	0	6	0	4	1	4	2	2	1	3	3	0	10	2	17	21	38	1712	55	44
N. R.	0	1	0	2	1	3	0	0	1	1	3	0	6	2	11	9	20	1675	45	45

TABLE IV

RELATION OF NUMBER OF PREGNANCIES TO MORTALITY
(ENTIRE GROUP)

	UNDER 1000 GM.		1000-1249 GM.		1250-1499 GM.		1500-1749 GM.		1750-1999 GM.		2000-2249 GM.		2250-2500 GM.		TOTAL		TOTAL	AV. WT.	TRUE % MORTALITY	EXPECTED % MORTALITY
	L.	D.	L.	D.	L.	D.	L.	D.	L.	D.	L.	D.	L.	D.	L.	D.				
0	0	19	1	12	14	9	25	18	48	13	73	12	161	8	323	91	414	2002	22	24
1	0	22	0	0	3	12	8	6	22	12	39	6	86	8	158	75	233	1940	32	29
2	0	14	0	6	4	5	7	6	9	7	19	1	37	3	76	42	118	1847	35	34
3	0	2	1	0	0	3	5	4	4	1	10	0	22	1	42	11	53	2012	21	22
4	0	5	2	1	1	4	3	2	2	2	4	2	14	0	26	16	42	1797	38	35
5	0	5	0	1	0	3	2	0	2	0	6	0	7	0	17	9	26	1745	35	40
More	0	6	0	9	3	3	7	2	8	2	6	2	15	2	39	26	65	1745	40	41

TABLE V

METHOD OF DELIVERY

	UNDER 1000		1000-1249		1250-1499		1500-1749		1750-1999		2000-2249		2250-2499		TOTAL			AVERAGE WT.	TRUE % MORTALITY	EXPECTED % MORTALITY
	L.	D.	L.	D.	L.	D.	L.	D.	L.	D.	L.	D.	L.	D.	L.	D.	T.			
Vertex	0	38	4	22	17	28	41	24	70	25	130	18	300	17	562	172	734	2005	23	24
Breech	0	23	0	13	5	12	12	10	19	11	23	3	41	7	100	79	179	1765	44	38
Transverse*	0	2	0	0	0	1	1	0	0	0	0	0	2	0	3	3	6	1557	50	53
Not reported	0	9	0	4	2	2	4	4	5	1	9	0	13	2	33	22	55	1737	40	40
Induced	0	8	0	9	6	10	18	9	18	8	20	5	33	3	95	52	147	1832	35	34
Medical*	0	2	0	1	0	4	6	0	6	1	2	0	7	0	21	8	29	1790	28	36
Bag	0	6	0	1	4	5	7	8	8	5	5	2	14	1	38	28	66	1777	42	37
Artificial rupture of membranes*	0	1	0	0	0	0	1	0	3	0	1	0	1	0	6	1	7	1767	14	40
Caesarean	0	4	0	3	1	1	3	1	5	1	8	3	16	1	33	14	47	1927	30	29
Version	0	0	0	6	0	1	3	0	4	4	6	0	13	1	26	12	37	1947	32	33
Forceps	0	1	1	0	2	4	3	2	8	2	12	0	43	1	69	10	79	2112	13	19

*General Hospital series only.

EFFECT OF FACTORS AT THE TIME OF LABOR ON PREMATURE MORTALITY

In Table V are tabulated the mortality rates of premature infants associated with some of the common factors at the time of delivery. To make comparison possible between factors, the expected mortality rates for each factor on a basis of weight is also tabulated. Although there is considerable variation in mortality between these groups, and, at first sight, it would seem that one method may seem decidedly better than another, if one inspects the expected mortality for each, it seems clear that the main factor is the difference in average weight of the infants comprising each group and not the method or type of delivery.

Presentation.—The "vertex" babies have a decidedly better chance of survival than do the "breech" babies, but the former weigh nearly 250 gm. more on the average, than do the breech infants, and this difference in weight largely accounts for the difference in mortality. However, the vertex infants have 0.75 per cent better chance of survival than would be expected on a basis of weight, while the breech infants have 6.5 per cent less chance of survival than would be expected on a basis of weight. Thus, the true difference, after accounting for weight difference between these two methods of presentation, as far as premature infant mortality is concerned, is 7.25 per cent. With the number of cases involved, and assuming no error for the estimate of the expected mortality, the chances are about one in ten that this is due to a sampling error.

Induction of Labor.—Although in the group in which labor was induced the mortality was 35 per cent, and in the group in which labor was not induced the mortality was 27.6 per cent (232 deaths among 860 infants), when weight is considered, neither one varies from its expected mortality by much more than 1 per cent. It would seem, therefore, that induction, of itself, has little effect on premature infant mortality.

However, if by induction of labor infants are brought into the world who are too small to survive, naturally this will affect adversely the general infant mortality rate. It is in this group of infants that we feel, in common with Clifford, that most can be done by the obstetrician. He is constantly confronted by two problems. The first is the question of inducing labor at the risk of the child for the sake of the mother; the second and equally difficult problem is the question of when to interrupt a pregnancy to save the child from death in utero at risk of death from prematurity. In the toxemias these questions are fairly common. In this study we have made no attempt to settle them. We merely point out that in our series 147 infants were delivered prematurely because of induction of labor. This represents

TABLE VI

EFFECT OF ANESTHESIA ON PREMATURE MORTALITY

	UNDER 1000 GM.		1000-1249		1250-1499		1500-1749		1750-1999		2000-2249		2250-2499		TOTAL			GROUP	AVERAGE WT.	TRUE % MORTALITY	EXPECTED % MORTALITY
	L.	D.	L.	D.	L.	D.	L.	D.	L.	D.	L.	D.	L.	D.	L.	D.	T.				
Ether alone		12		5	6	4	16	2	15	2	28	1	69	5	134	31	165	1.42	1980	19	26
Nitrous oxide alone		2		1	1	3	2	2	7	2	8	2	14	2	32	14	46	1.39	1972	30	26
Sodium amytal and ether		3		3	1	5	4	2	6	3	12		25	2	48	18	66	1.38	1970	27	26
Sodium amytal, scopolamine, ether					1	2	2	2	6		12		36	2	57	6	63	2.24	2180	10	15
None		10	1	9	3	6	6	7	14	10	13	5	30	4	67	51	118	0.83	1832	43	34
Morphine combined		6		2		4	2	4	3	2	13	2	20	3	38	23	61	1.22	1930	38	28

approximately 15 per cent of the premature infants, and, if these infants could be carried further toward term without undue risk to the mother or without materially increasing the stillborn rate, we might improve the infant mortality rate.

If we study the means of induction, it is found that there is almost 14 per cent difference between the mortality rate of infants delivered after induction medically as compared with those in which a bag was used to start labor, and this difference is in favor of medical induction. When weight is accounted for, this difference remains. However, with the small number of cases involved the statistical error is relatively large. If we again assume no error for the calculation of the expected mortality, the chances are about 15 in 100 that this difference is due to chance sampling. This suggests, but does not prove, that between these two means of induction, as far as the child is concerned, medical induction is safer.

Caesarean section, in contrast to the findings of Clifford's original series, did not, in our series, exert any deleterious effect on the infant which could not be accounted for on a basis of weight.

Version extractions, although the series is extremely small, had no adverse effect on the premature mortality rate.

Forceps delivery has a mortality of 12.65 per cent as compared with an expected mortality for weight of 19 per cent. This difference of 6.45 per cent in favor of forceps delivery, if we assume no error for the expected mortality, has approximately 8 chances in 100 of being due to sampling. This suggests rather strongly that forceps delivery is a very safe manner of delivering premature infants.

Anesthesia.—Our figures for the effect of anesthesia are gathered from the General Hospital series only (Table VI). In calculating the expected mortality, the figures from that hospital were therefore used alone. Since these figures cover a smaller number of cases, the error in the expected mortality is probably higher than when the combined series figures are used.

The variables encountered here, such as duration of anesthesia, time of anesthesia in respect to delivery, amount of anesthetic, amount of other drugs, combinations of drugs, etc., was so great that we cannot feel that the figures are particularly reliable. Where one drug alone was used, such as sodium amytal, the cases were so few that the figures were entirely unreliable. The list which we obtained represented the more commonly used means of relieving pain at the time of delivery. They are tabulated in Table VI.

If we tabulate these findings from the safest to the most dangerous we obtain Table VII. No correction is made for error in calculating expected mortality.

TABLE VII

	EXPECTED MORTALITY %	TRUE MORTALITY %	SIGMA TRUE MORTALITY %	DIFFERENCE IN MORTALITY %	PROBABILITY IN 100 DUE TO SAMPLING
Ether alone	25.9	18.8	±3.06	7.1	2
Ether, sodium amytal, scopolamine	14.6	9.5	±2.66	5.1	5
Sodium amytal, ether	26.4	27.3	±5.43	0.9	87
Nitrous oxide plus O_2 alone	25.6	30.5	±6.75	4.9	46
None	34.5	43.1	±3.5	8.6	1
Morphine combined	28.0	37.9	±5.75	9.9	8

From Table VII it would appear that the safest anesthesia is ether, the most dangerous, morphine (although the morphine was usually combined with other drugs). The other drugs seem intermediate. The difference in mortality between ether and morphine is 17 per cent. Surprisingly enough, the mortality is higher than with any anesthesia except morphine, when no anesthesia is given to the mother. We have no explanation for this finding.

SUMMARY AND CONCLUSIONS

A statistical study of the influence of factors in the mother and in the obstetric management of premature deliveries on premature infant mortality is presented, based on a study of 987 premature infants. Size at birth is the most important factor influencing mortality of premature infants. In this study weight at birth is used as the criterion of size.

In order to evaluate the influence on premature mortality of factors other than size at birth, it is imperative that a method for eliminating the influence of weight in the analysis be used. Such a method is presented.

When the influence of weight at birth on mortality is eliminated, it is found that the following facts are suggested:

Conditions in the mother such as multiple pregnancy, toxemia, etc., have relatively little effect on the mortality of the premature infant who is born alive. The one marked exception to this is hydramnios, which exerts a very harmful effect on the premature infant mortality rate.

The age of the mother has very slight effect on premature infant mortality except in women over forty years of age whose infants have a slightly higher mortality rate than we should expect on a basis of weight.

Vertex delivery is slightly safer than breech delivery.

On the whole induction of labor has no deleterious effect on premature infant mortality. Medical induction seems safer than induction by bag.

Caesarean section seems to be a safe method of delivery of premature infants.

Forceps delivery seems safer than any other means of delivery of the premature infant.

Ether seems the safest anesthetic as far as the child is concerned. The use of morphine with other drugs is dangerous. Next to the use of morphine, the use of no anesthetic was associated with the highest mortality rate in premature infants.

From a practical standpoint the most important group to consider in reducing the prematurity mortality rate by proper obstetric management will be in the group of infants whose deliveries were induced —in our series 15 per cent of the total. If in some way these infants could be brought nearer term, the mortality might be reduced. However, improvement here can at best be expected to be only slight, since the obstetrician is often confronted with the problem of having a stillborn infant or a dead mother unless he resorts to induction.

From the practical standpoint, unless we can somehow manage to have larger infants, the use of one method of delivery in preference to another will exert relatively little effect on the premature mortality rate. It would seem that our best hope of improvement in premature mortality rate still lies in the care of these infants after birth, although any method of obstetrics which tends to bring smaller infants into the world by means of induction, when they might safely stay in utero, will increase the general infant mortality rate.

Invaluable advice in the statistical handling of this material was offered by Prof. Jack Dimlop and Prof. Donald Gilbert, of the University of Rochester.

REFERENCES

1. Hess, Julius H.: J. A. M. A. **107**: 400, 1936.
2. Clifford, Steward: J. PEDIAT. **5**: 2, 1934.
3. Clifford, Steward: Surg. Gynec. Obst. **58**: 727, 1934.
4. Clifford, Steward: Ibid. **58**: 959, 1934.
5. Clifford, Steward: J. A. M. A. **103**: 1117, 1934.

Critical Review

INFECTION AND IMMUNITY

Critical Review of Experiments Tending to Show the Cause and Mechanism of Infection and Immunity in Erysipelas

John A. Toomey, M.D.
Cleveland, Ohio

ERYSIPELAS has long been differentiated from other infectious diseases. Even Hippocrates described it as a clinical entity. It has also long been known that in this disease the skin or mucous membranes and their lymphatic vessels are involved. The causes ascribed to erysipelas have been as varied and as numerous as the number of writers describing them. In 1882 Fehleisen[1] excised small pieces of skin from erysipelas lesions, planted them in gelatin broth, and isolated streptococci. He also found these organisms in the bullous lesions often associated with this infection. Because he believed these streptococci to be specific for this disease, he termed them *Streptococcus erysipelatis.*

Although Fehleisen produced the disease in rabbits, others could not always confirm his results. It was often found that some strains of erysipelas streptococci were virulent for man and not for rabbits, while some strains produced discrete lesions in the animals and others, phlegmonous ones. To add to the confusion, streptococci were also isolated from other diseases. In 1884 Rosenbach[2] first found streptococci in pus and called these organisms *Streptococcus pyogenes.* Soon the term *Streptococcus erysipelatis* was dropped and all streptococcic organisms came to be classified as *Streptococcus pyogenes.* The older experiments with streptococci gave variable results. The local reactions were variable; the organisms themselves were variable in their characteristics and were found associated with other diseases. Petruschky[3] found that streptococci, ostensibly *Streptococcus pyogenes,* isolated from pus could cause erysipelas in the human being. In 1907 Muir and Ritchie[4] concluded that there was no clear-cut distinction between *Streptococcus erysipelatis* and *Streptococcus pyogenes.* It was only clear that streptococci were usually present in erysipelas. It must be mentioned in passing that not all cases of erysipelas are caused by streptococci. Staphylococcus, pneumococcus, *B. coli* and *B. typhosus,* etc., have all been isolated from erysipelas patients, and the disease has been experimentally produced by these organisms. This is mentioned merely to call it to mind. This discussion will be limited to the streptococci usually found to be the causative factor.

The later results in experimental erysipelas have been summarized by Gay[5] and Gay and Rhodes.[5a] In 1925 Rivers[6] and Rivers and Tillett[7] were able to produce erysipelas lesions in the skins of rabbits by injecting intracutaneously streptococci isolated from erysipelas patients. They obtained two types of lesions, a phlegmonous reaction and a spreading red reaction. Birkhaug[8] produced erysipelas lesions in rabbits by inocu-

From the Department of Pediatrics, Western Reserve University and the Division of Contagious Diseases, City Hospital, Cleveland.

lating them intradermally with specific agglutinable strains of *Streptococcus erysipelatis*. He produced three types of lesions: erythematous, diffuse, and phlegmonous.

Mackie and McLachlan[9] could not demonstrate much difference between streptococci, since streptococci from various sources produced erysipelas in animals, provided the virulence of the organisms was modified by passage. They believed that one and the same strain could produce suppuration, erysipelas, or septicemia.

Although all agreed that the streptococci initiated most cases of erysipelas, it became a moot point as to whether the erysipelas streptococci were specific. Birkhaug[10] believed that they were. He attempted to show biologic differences between streptococci isolated from erysipelas and from other diseases. Many laboratory tests have been designed to show specificity, such as opsonic test, complement fixation test, precipitin test, agglutination and agglutinin absorption test. No definite conclusion has ever been reached regarding opsonic tests, and the complement fixation test has been of questionable value. Birkhaug in 1928 stated that although the reactions to the complement fixation test gave promising results as to type specificity, further tests would have to be done before it could be relied upon. He felt, however, that by the use of agglutination and agglutinin absorption tests specificity could be demonstrated. Krumweide and Valentine[11] and Hitchcock[12] did not hold the same opinion. Birkhaug in reviewing the immense work on classification of hemolytic streptococci was struck by the fact that differences between groups of streptococci had not been convincingly established by morphology, sugar fermentation, hemolysis, opsonification, complement fixation, and precipitin reactions. He then attempted to show differences in straight absorptive agglutinability which would tend to show specificity. Of 34 erysipelas strains, 31, or 91.2 per cent, were agglutinated by absorption with each of seven immune erysipelas serums. Of 45 miscellaneous strains, only 9, or 20 per cent, showed agglutinability. Dochez and Stevens[13, 13a] felt that even with most careful work in preparing the streptococcal antigens and the antigen antibody serums, there were variations with different strains and different serums. They concluded that it was impossible to differentiate some scarlet fever strains from erysipelas strains by the process of agglutinin absorption. These workers felt that the differences which might be present occurred only in specific antigenic fractions which thus far have not been isolated and refined. Williams[14, 15] could not confirm Birkhaug's work on agglutination. She even suggested that the name *Streptococcus erysipelatis* be discarded as well as the term *Streptococcus scarlatinae* and that all of such types of streptococci be grouped under the name *Streptococcus hemolyticus*.

Because of adverse criticism regarding the results on specificity by agglutinin and absorption of agglutinin tests, Birkhaug tried to demonstrate antigenic relationships by in vivo experiments. He concluded that as little as 0.005 c.c. of erysipelas serum protected against 0.1 c.c. of homologous organisms, while it took 0.01 c.c. of immune serum to protect against 0.1 c.c. of heterologous organisms. This is a repetition or a modification of Besredka's fundamental antiviral experiments. Instead of applying the antivirus material to the skin as a specific dressing, Birkhaug injected it intradermally. It has been shown, however, that the specific dressings of Besredka are not needed for protection. Toomey

and Freedlander[16] have demonstrated that this protection in the skin may be brought about by local applications of nonspecific materials. Anything which contained peptone broth was as efficacious in protecting guinea pigs against local infections of staphylococci and streptococci as were the specific substances in which the organisms grew. Gay and Morrison[17] have also shown that the protection is nonspecific. Freedlander and Toomey[16a] felt that the protection obtained against staphylococcus was the result of local mobilization of the clasmatocytes and not to any humoral antibody. They showed the whole procedure to be nonspecific in character.

Thus, it can be stated that the specificity of erysipelas strains of streptococci is at the present time doubtful and that the published experiments have not definitely established the fact that separate strains of erysipelas streptococci exist.

As early as 1888 it was known that a toxic filtrate was produced by the *Streptococcus erysipelatis*. Birkhaug[18] demonstrated that streptococci isolated from erysipelas produced toxins. His findings were confirmed by Eagles[19] and Andrewes,[20] Dochez and Stevens[13] and the Dicks.[21] Eagles and Andrewes, however, did not prove that different streptococci formed different toxins. Dochez and Stevens were unable to demonstrate complete specific differences in streptococci obtained from scarlet fever and from erysipelas. The Dicks, however, concluded that the toxins from scarlet fever and erysipelas streptococci were different. Singer and Kaplan[22, 23] obtained complete neutralization of erysipelas toxin with heterologous antitoxins (i.e., scarlet fever antitoxin against erysipelas toxin) in one-fourth of their cases. This would indicate a lack of absolute specificity. Likewise, erysipelas antitoxin neutralized equal quantities of diluted scarlet fever toxin. They concluded that neither erysipelas nor scarlet fever streptococci were biologically specific. They stated, however, that these results were obtained with only two strains of streptococci.

Toomey and Martin[24] have grown three strains of erysipelas streptococci, Nos. 766, 767 and 769, carried in the American type culture collection in 0.5 per cent glucose broth. A fourth strain was contaminated. We have likewise grown Dochez No. 5 (No. 4014, American type culture collection) and the two Dick scarlet fever strains (Nos. 543 and 4075), obtained from the same source and four strains obtained from unrelated diseases. All of these organisms produced toxins. The Dick and the Dochez strains produced a high titered toxin within forty-eight hours. The erysipelas strains also produced high titered toxins, but it took longer to produce a good toxin, i.e., from six to ten days. If all toxins produced by every streptococcus were harvested within forty-eight to seventy-two hours, there would be a marked difference in toxin production; a difference which would not be so obvious if each organism were allowed to grow its optimal time for toxin production.

Smith[25] concluded that all strains of hemolytic streptococci produced exotoxins, and Parish and Okell[26] could not see specific differences among toxins produced by hemolytic streptococci of diverse origins.

Birkhaug used the skin test to demonstrate specificity. He tested a number of children in 1926 with the Dick toxin and erysipelas toxins. Among the groups tested, 52 per cent had positive Dick tests, 24 per cent were negative to erysipelas toxin, and 10 per cent were positive to both

toxins. From these figures, he drew the conclusion that there was a difference between the two streptococcal groups comparable to the serologic differences. His toxins, however, were harvested simultaneously: each organism did not grow its optimal time. Paraf[27] and Eagles[19] compared reactions obtained from toxins from scarlet fever and nonscarlatinal sources. They concluded that the latter differed from the former only in the amount of toxin present. Williams and her coworkers[14] carried out skin protection and exotoxin neutralization tests and found cross protection and cross neutralization with antierysipelas and antiscarlatinal serums. Thus, although the disease could be caused by a streptococcus, there was no evidence that it was specific; and, although a toxin was produced, there was no evidence that it was specific.

It is clear, however, that a toxin is produced by the various strains of streptococci isolated from erysipelas, but it is not definite whether these strains can be separated from or differentiated from strains isolated from pus or from other sources, such as scarlet fever. Birkhaug isolated toxins from the blood and urine of patients ill with erysipelas. The symptoms of the disease and the high temperatures present in the disease were claimed to be the secondary reactions to the toxin produced. In short, the streptococci gained entrance into the host at the area where the erysipelas started and produced toxins which caused the general reactions accompanying the disease. In a consideration of second attacks of erysipelas and skin tests, Birkhaug found that recurrent attacks occurred in 7.3 per cent of 342 cases and that during the acute stages of the attack the patient was positive to skin tests. He believed that he demonstrated that there was a gradual increasing amount of antitoxin in the blood serum of the patients to a time when the skin test became negative. This active immunity appeared in about six weeks, as shown by the skin tests, and, when the patient's blood was tested at this time, there was an absence of antitoxic substance. This explanation does not square with clinical or with experimental evidence. For the mechanism of skin sensitivity, one has to refer to the experiences of Dochez and Stevens.[13, 13a] They noted that rabbits injected with toxic filtrates in immunization procedures passed through successive periods of sensitization until they finally developed into a stage of continuous sensitization. It would appear that such sensitization followed the injection of the bodies of bacteria and their extracts and was brought about long after immunization had started. They experienced two types of skin reaction: one, an early one neutralizable by immune serum and probably due to hypersusceptibility; the other, a later stage of true skin sensitivity not neutralizable by immune serum. They suggested, in view of the allergic reactions observed in animals made hypersusceptible to scarlet fever and erysipelas streptococcus strains, that the positive cutaneous reaction with the streptococcic filtrates containing the toxin fraction in erysipelas, as well as the rash in scarlet fever, were the result of previous sensitization with the respective bacteria. As far as scarlet fever is concerned, Cooke[28] also agrees with this point. One need not agree with all deductions of these workers, but one cannot escape the facts. Dochez and Stevens have definitely proved that animals are sensitized to the toxic products of erysipelas, and they raised the question of allergic sensitivity as a possible basis for the phenomenon of erysipelas. Their explanation fits the clinical picture better than does Birkhaug's theory as to local infection and generalized toxicity.

Supplementary studies, studies which to my knowledge have never been contradicted or refuted by clinical or experimental evidence, have been made by Francis.[29] He summarized Birkhaug's work as follows: "Hemolytic streptococci from erysipelas were found to form an immunologically specific group of streptococci. Ninety-one per cent of such organisms tested by the agglutinin absorption technique fell into this group. No cross agglutination with *Streptococcus scarlatinae* was noted. Serum obtained by immunizing rabbits against strains of erysipelas streptococci protected the skin of normal rabbits from infection with the homologous and heterologous erysipelas strains when the serum and bacteria were injected together. Passive immunity was also obtained by intravenous or subcutaneous injection of the serum twenty-four hours before the inoculation of a supralethal dose of organisms. Under these conditions the results with heterologous organisms were not so regular as with the homologous strains. The immune serum caused a blanching of the erysipelatous lesion in patients or tended to prevent its spread. This effect was not obtained with scarlatinal antitoxin; nor was blanching of the scarlatinal rash obtained with antierysipelas serum. Blanching of the erysipelatous lesion was also obtained with convalescent erysipelas serum. Broth cultures of erysipelas streptococci uniformly gave toxic filtrates which in dilutions of 1:1,000 produced a skin reaction in susceptible individuals similar to a positive Dick test. Some strains produced filtrates which contained 30,000 to 50,000 S.T.D. of toxin per cubic centimeter. It was noted that the maximum production of toxin was obtained with forty-eight hours' incubation and that a definite decrease in the amount of toxin occurred after ninety hours. The cutaneous reaction produced by 1 S.T.D. could be completely neutralized by mixing the skin test dose with an equal amount of convalescent erysipelas serum, or with 0.001 c.c. of erysipelas antistreptococcic rabbit or donkey serum. Eighteen patients with erysipelas gave positive reactions to 1 S.T.D. of toxin on admission to the hospital, and, as the erysipelatous lesion cleared and convalescence was established, the reactivity of the skin to a similar dose was lost. This occurred from five to thirty-eight days after the original test. During the acute stage of erysipelas when skin reactions were positive, there was demonstrable in the patient's serum a toxic substance which caused a local cutaneous reaction in normal susceptible individuals. This reaction could be neutralized by immune or convalescent erysipelas serum. A toxic substance occurred in large amounts in the urine. With the disappearance of the cutaneous susceptibility to the toxin, following recovery from the disease, the presence of antitoxin in the serum of patients was demonstrated by means of toxin neutralization tests in the skin of susceptible individuals. Cross neutralization of the erysipelas toxin by scarlatinal antitoxin was not obtained. Antierysipelas donkey or rabbit serum produced favorable therapeutic results when given early in the disease. The impression obtained was that the serum was antitoxic in nature." Most of these points have been previously commented upon in this review.

Francis investigated three fundamental aspects of the subject. These were (1) the reactivity of the skin of erysipelas patients to intracutaneous injections of filtrates of erysipelas streptococci; (2) the presence of a toxic substance in the blood of patients acutely ill with erysipelas; and (3) the capacity of the serum of patients ill with erysipelas to neutralize the toxic action of culture filtrates.

The repeated tests in the later acute period of the disease and during convalescence showed a general, although not uniform, tendency for the reactivity of the skin to increase rather than to decrease and become negative as reported by Birkhaug.

The great majority of Francis' cases fell into the group (Group I) in which the sera, collected early in the acute stage of the disease, completely or partially neutralized the toxic action of the filtrate. In only eight cases of another group (Group II) did the early bleedings fail to neutralize. Another very striking result Francis obtained was the failure of the late convalescent serum to neutralize toxin at all. Not only was there a failure of the convalescent serum to neutralize, but in many instances a more marked reaction occurred than with the filtrate alone, a type of enhancement as noted after injecting specific antibody antigens in sensitized individuals.

In his discussion he stated that the three important phenomena brought to light in the preceding observations [namely, (1) the tendency for the cutaneous reactivity of erysipelas patients to become more marked during convalescence, (2) the absence of a demonstrable toxin in the circulating blood of patients in the acute stage of the disease, and (3) the neutralization of erysipelas streptococcus culture filtrates by the sera of most patients in the acute phase of the disease with apparent loss of this power during convalescence] fail to support Birkhaug's concept of erysipelas as a specific toxemia, recovery from which is due to the development of an antitoxic immunity.

Further, the results of the skin tests suggest that an increasing sensitiveness or allergy to the products of streptococci presumably liberated at the site of the erysipelatous lesion develops with the progress of the disease to convalescence and recovery. The fairly definite correlation between the rapidity with which reactivity developed and the clinical course of the disease, as shown in one of his charts, furthermore suggests that the development of tissue allergy may play at least a part, perhaps an important part, in the mechanism of recovery from the infection. That the skin reactions were neutralizable not only in sensitive normal individuals but also in sensitive patients in the convalescent period, as proved to be the case in a number of tests, is not surprising since it has been shown by Dochez and Stevens that the skin reactions of rabbits rendered allergic to undiluted culture filtrates of erysipelas streptococci are neutralizable during the early phase of sensitivity. He quotes Besredka and Nakagawa as stating that the cutaneous mechanism of defense is not, in general, associated with circulating antibodies.

Because of the observation presented, Francis felt that it was justifiable to conclude that the pathogenesis of erysipelas is not comparable to the pathogenesis of the specific toxin phase of scarlet fever; that the mechanism of recovery from erysipelas, in adults at least, is not a simple neutralization of a circulating toxin through the development of antitoxin, but rather that it is more intimately related to the development of allergy to products of the growth and dissolution of streptococci in the erysipelatous lesion. Furthermore, the failure to find toxin in the blood and the usual presence of a neutralizing antibody in the early acute stage of the disease provide little basis for the view that antitoxin in treating adults ill with erysipelas should be of particular value in erysipelas. It is equally obvious that convalescent serum would be of no greater value.

The experiments of Dochez and Stevens and Francis definitely place this disease on an allergic basis. Their experiments and conclusions have not been challenged to date.

I have not done extensive research work along this line, but to satisfy my curiosity a few cases of erysipelas have been tested in the same manner as outlined by Francis. The results in those few cases, ten in number, were the same as his.

Birkhaug[30] quotes Zinsser[31] on the significance of bacterial allergy. The latter author stated that "it is important to consider the possibility that sensitization to an organism which so frequently invades the human throat may take place and may give rise to an allergic condition to which many of the manifestations of scarlet fever could be attributed." I think that this statement could apply to erysipelas though not to scarlet fever. Certainly the allergic hypothesis is the most plausible one and the one which comes nearest to fitting the facts in this disease. Birkhaug admits that a state of bacterial allergy may possibly play an important rôle in certain cases of recurrent attacks of erysipelas and by implication refers to it as possible Arthus phenomenon.[32] This theory of sensitization likewise fits the facts better than that of Durham,[33] who felt that a particular strain of erysipelas streptococcus predominated at one time and then another latent one at another time. He thought that, by a sudden liberation of toxic substances during the active phase of growth of the secondary invaders, a relapse took place. He also felt that such processes could be repeated indefinitely. The theory need only be mentioned to be discarded, as it has never been seriously considered as a true explanation of the clinical phenomena as they exist in erysipelas.

The laboratory evidence as to specificity of streptococci, specificity of toxin, specificity of tests and mechanisms has not been confirmed by experimental evidence. Clinical evidence was then proffered and deductions made therefrom. The conclusion was drawn that erysipelas streptococci were different from the streptococci causing other conditions because the diseases produced were different. As an example, it was stated that erysipelas is more contagious than cellulitis, both of which may be caused by streptococci. It seems that it would be more important to know whether a single streptococcus strain could cause both of these conditions. Streptococci could cause erysipelas when injected in the skin of rabbits; cellulitis if injected subcutaneously, possibly an osteomyelitis if injected subperiosteally, bacteriemia if injected into the blood stream, and sometimes multiple abscesses following local injections. We have seen all these conditions in one and the same patient. One organism may give many clinical reactions, depending on its localization. It cannot be said that the statement that erysipelas is more contagious than cellulitis is a good reason for differentiation. It need not even be considered seriously, for neither condition is considered very contagious in nature. Individuals do not contract erysipelas from cases of erysipelas per se. They might contract the upper respiratory infection or the local infection that the erysipelas patient has and subsequently, erysipelas, or they may transmit the organisms from a case of erysipelas or cellulitis on their fingers and give themselves erysipelas by scratching these organisms into the skin. One of the reasons that cellulitis does not cause more infections is because the areas of cellulitis are treated surgically, kept clean, and there is small chance for transmission of infection. In fact there is

no direct contact or handling at all. It might be stated that, if there were no handling of erysipelas, there would be practically no spread of the disease. Over 2,000 cases of erysipelas have been admitted to our wards since 1920, and only one case of erysipelas has developed in the personnel. This individual, a nurse, had the usual preceding upper respiratory infection, and her presence on the contagious floor and her exposure to the patient with erysipelas were merely coincidental.

The Dicks[34] state that erysipelas follows infections of the upper respiratory passages and seldom follows scarlet fever. Among 7,386 cases of scarlet fever admitted to the Contagious Disease Hospital of Cleveland, between 1929 and 1937, erysipelas has developed in 14 instances. It is stated that erysipelas follows colds more frequently than not! Does it? How many more people have colds and upper respiratory infections than have scarlet fever? Millions. The mathematical proportion of those who develop erysipelas following colds might be even less than that proportion following scarlet fever. Much more suggestive is the fact that erysipelas rarely precedes scarlet fever. We have seen only 2 such patients—both of which had doubtful cases.

Appiani[35] also found that erysipelas could occur after scarlet fever. This is what one would expect if the logic of Dochez and Stevens and of Francis were accepted. There is every reason to believe that individuals who are sensitized to streptococci, especially those who have had scarlet fever, might become sensitized and develop erysipelas. How else would one explain the erysipelas which develops about empyema wounds, mastoid wounds, abscess wounds?

Birkhaug stated that the weightiest argument against suggesting that erysipelas and scarlet fever are caused by related strains is that scarlet fever manufactures immunity, whereas erysipelas predisposes to attacks. Schottmüller,[36] who agreed with Birkhaug, called attention to the highly specific infectiousness of scarlet fever as distinguished from erysipelas and other streptococcic infections. The deductions drawn by these workers do not follow.

Any streptococcic infection, if it is in the throat, whether it is an ordinary streptococcus sore throat, septic sore throat, or scarlet fever, is more likely to be spread than is a streptococcic infection that is hidden under the skin or in a wound. Such organisms in the upper respiratory passages are sneezed or coughed into the air, or the moist infected spittle comes in contact with objects, thus easily transmitting the organisms indirectly. Organisms are not held and bound down as in surgical diseases. Erysipelas itself is not a disease that exudes streptococci. Unless there are blebs, it is very difficult even to demonstrate the presence of streptococci without actually cutting into the skin. An attack of scarlet fever confers immunity against the toxins of the disease, but there is some question as to whether it protects against the streptococci that produce the toxins. The two diseases are not comparable. The scarlet fever patient has never had the disease before. In erysipelas we have a condition wherein an individual has been sensitized to the products of the streptococci. Another attack occurs when the antigen gets into the skin; the same as would happen in any allergic individual exposed to an antigen to which he is sensitive. Since patients ill with erysipelas have plenty of antitoxin in their blood stream at the height of the disease, it is not toxicity that causes the reactions associated with the disease.

The very fact that they have immunity and yet have relapses suggests an allergic condition. This is an entirely different mechanism of production than may be had with scarlet fever although the streptococcus is the etiological agent in both instances.

As far back as 1895 Cobbett and Melsome[37] concluded that cutaneous erysipelas conferred absolute local immunity, less constant general immunity; that both local and general immunity were of only a few weeks' duration, and that, when streptococci were introduced into immunized rabbits, an inflammatory erysipelas reaction quickly appears and usually subsides before inflammation has made any progress in the control animal. It was noted that when dead streptococci were introduced, they obtained the same reaction. Thus, these workers also demonstrated allergy even though its significance was not entirely understood or recognized.

Amoss and Bliss[38] found that, after recovery from intradermal inoculations of a given strain of hemolytic streptococcus, there was more resistance to succeeding injections of the same strain and the degree of local tissue resistance increased progressively with repeated inoculations. Dochez[39] again in 1928 reported on local hypersensitiveness. Birkhaug, commenting on hypersensitiveness, stated that, as long as erysipelas toxin was demonstrable in the patient's blood serum, the patient would remain locally hypersensitive to the intradermal injection of erysipelas toxin, but this reactivity tended to disappear when antitoxin was formed during convalescence. He also claimed that the patient became hypersensitive to the products of intradermal injections of toxic filtrates when specific antibodies disappeared from the blood.

Symmers and Louis[40] believed that the disease was a constitutional one and the body rash merely an objective phase of the infection; they concluded that local applications were valueless to control it. It may be admitted that the causative factor in this disease is streptococci in the most instances. It may be even admitted that the toxins of the streptococci are neutralized in the antitoxin made from the streptococci, but it does not follow from this that these toxins are the cause of the concomitant general disease, although they and their organisms cause the local lesion and, per se, initiate the disease. The scientific evidence is against the concept that patients ill with erysipelas lack immunity to toxin. If antitoxin were a factor in prevention, then no one should get erysipelas, especially those who have already had one attack of the infection; they are the ones who usually have plenty of neutralizing antibodies in the blood stream at the very height of the eruption. In other words, the patients are actually immune to the toxin at the time they get the disease.

It has been my clinical impression that erysipelas is a disease occurring in persons who have had many previous attacks of upper respiratory infections, sinusitis, colds, etc., and that it occurs in individuals who had plenty of immunity against the toxins of the organisms that caused the erysipelas, but who because of their frequent attacks of previous infections, such as colds, have become sensitized to streptococcic bacteria and their nucleoproteins. For years I have done Dick tests on the student nurses who have entered our training school.[42] The general average of positive reactors among those who come from urban areas is approximately 35 per cent, while the total number of positives may be as

high as 65 per cent for the students coming from suburban areas. In 1927 I began to have Dick tests made on patients with erysipelas admitted to the hospital. Theoretically from 35 to 65 per cent of the individuals should have had positive Dick tests. The controls could be the nurses that were tested at the same time. Between 1927 and 1938, 1,288 patients with erysipelas were tested and only 99 patients with erysipelas had positive Dick tests. In other words, only 7.6 per cent of these subjects were susceptible to one skin test dose of scarlet fever streptococcus toxin, whereas in a comparable group, from 450 to 837 individuals would have been positive. It was significant that such a low reaction rate would appear in this group of individuals. It suggests a group of patients with some immunity to streptococcic toxins.

Spink and Keefer[43] found only one erysipelas patient in 50 who had responded to the Dick toxin. They reported the interesting fact that 24 of the patients with erysipelas who were tested showed responses to the nucleoproteins of the hemolytic streptococci. This is what one would expect if it is to be considered that this disease is allergic in nature and due to the release of the protein factors. They stated that the bactericidal power of streptococci may be increased or stationary during an attack of erysipelas. It must be understood that resistance may be depleted and streptococci may spread from local lesions, giving rise to the complications which may be the cause of death.

The clinical test of sulfanilamide is of some value in that the drug does not have any effect upon disease states caused by streptococcus toxins. We have found it to be of no value in the fulminating case of meningitis or in the toxic type of scarlet fever. It does help clear up the septic type of epidemic meningitis which is the usual type admitted to the hospital and has a favorable influence upon the septic and later complications of scarlet fever. However, its effect on erysipelas is striking. This again suggests the fact that the organisms or the nucleoproteins of the hemolytic streptococci cause the reaction. Finally, if erysipelas were due to a toxin, patients should react favorably to erysipelas antitoxin. It has not been shown that erysipelas antitoxin is of value in controlling the spread of the infection.

If erysipelas is a sensitivity phenomenon and if the local reaction is compared to a massive phenomenon occurring in an individual who has been previously sensitized to the streptococci and their proteins, how can one explain the disease in the infant? This is simple when it is realized that the infant may carry over from the placental blood, not only immune bodies, but also the sensitizing factors of the mother which would temporarily make him likewise passively rather than actively sensitized as in the case of the adult. Since in the baby immunity against the toxins is passive, it would be easily depleted, and the death rate would be high as it is. In this type of case antitoxin has proved to be of some value. One might tentatively conclude and deduce from the evidence that erysipelas is a disease which occurs only in individuals who have been previously actively or passively sensitized to streptococci and their protein products; in individuals who ordinarily have, at the time of their infection, plenty of antitoxin in the blood stream; in individuals who react at the point of entrance of the streptococcus organism with a massive Arthus phenomenon.

REFERENCES

1. Fehleisen: Deutsche med. Wchnschr. **8**: 553, 1882.
2. Rosenbach, A. J. F.: Mikro-organismen bei der Wundinfektionskrankheiten des Menschen, Wiesbaden, Chap. 22.
3. Petruschky, J.: Ztschr. f. Hyg. u. Infektionskr. **17**: 59, 1894; **18**: 413, 1894.
4. Muir, R., and Ritchie, J.: Quoted in Annals of Picket Thomson Research Laboratory **5**: 6, 1931.
5. Gay, F. P.: Physiol. Rev. **4**: 191, 1924.
5a. Gay, F. P., and Rhodes, B.: J. Infect. Dis. **31**: 101, 1922.
6. Rivers, T. M.: J. Exper. Med. **41**: 179, 1925.
7. Rivers, T. M., and Tillett, W. S.: J. Exper. Med. **41**: 185, 1925.
8. Birkhaug, K. E.: Bull. Johns Hopkins Hosp. **37**: 307, 1925.
9. Mackie, T. J., and McLachlan, D. G. S.: J. Hyg. **27**: 225, 1928.
10. Birkhaug, K. E.: Bull. Johns Hopkins Hosp. **36**: 248, 1925.
11. Krumweide, C., Jr., and Valentine, E. L.: J. Immunol. **6**: 343, 1921.
12. Hitchcock, C. H.: J. Exper. Med. **40**: 445, 1924.
13. Dochez, A. R., and Stevens, F. A.: J. Exper. Med. **44**: 439, 1926.
13a. Idem: Ibid. **46**: 487, 1927.
14. Williams, A. W., et al.: Arch. Path. & Lab. Med. **4**: 481, 1927.
15. Williams, A. W.: Am. J. Pub. Health **19**: 1303, 1929.
16. Toomey, J. A., and Freedlander, S. O.: J. Exper. Med. **53**: 363, 1931.
16a. Freedlander, S. O., and Toomey, J. A.: J. Exper. Med. **47**: 663, 1928.
17. Gay, F. P., and Morrison, L. F.: J. Infect. Dis. **33**: 338, 1923.
18. Birkhaug, K. E.: Proc. Soc. Exper. Biol. & Med. **23**: 201, 1925.
19. Eagles, G. H.: Brit. J. Exper .Path. **7**: 286, 1926; **8**: 403, 1926.
20. Andrewes, F. W.: St. Barth. Hosp. J. **33**: 181, 1926.
21. Dick, G. F., and Dick, G. H.: J. A. M. A. **93**: 1784, 1929.
22. Singer, H. A., and Kaplan, B.: J. A. M. A. **87**: 2141, 1926.
23. Singer, H. A., and Kaplan, B.: Arch. Path. & Lab. Med. **2**: 461, 1926.
24. Toomey, J. A., and Martin, M. W.: Unpublished experiment.
25. Smith, J.: J. Path. & Bact. **30**: 651, 1927.
26. Parish, H. J., and Okell, C. C.: Lancet **1**: 746, 1928.
27. Paraf, J.: Bull. et mém. Soc. méd. d. hôp. de Paris **49**: 395, 1925.
28. Cooke, J. V.: Am. J. Dis. Child. **35**: 991, 1928.
29. Francis, Thomas, Jr.: J. Clin. Investigations **6**: 221, 1928-29.
30. Birkhaug, K. E.: J. A. M. A. **90**: 1997, 1928.
31. Zinsser, H.: Bull. New York Acad. Med. **4**: 351, 1928.
32. Arthus, M.: Compt. rend. Soc. de biol. **55**: 817, 1903.
33. Durham, H. E.: J. Path. & Bact. **7**: 240, 1901.
34. Dick, G. F., and Dick, G. H.: J. A. M. A. **89**: 1135, 1927.
35. Appiani, G.: Gazz. d. osp. **29**: 1228, 1908.
36. Schottmüller, H.: Klin. Wchnschr. **6**: 1692, 1927.
37. Cobbett, L., and Melsome, W. S.: J. Path. & Bact. **3**: 39, 1895.
38. Amoss, H. L., and Bliss, E. A.: J. Exper. Med. **45**: 411, 1927.
39. Dochez, A. R.: J. A. M. A. **91**: 51, 1928.
40. Symmers, D., and Louis, K. M.: J. A. M. A. **89**: 880, 1927.
41. Symmers, D.: J. A. M. A. **91**: 535, 1928.
42. Toomey, J. A.: Ann. Int. Med. (in press).
43. Keefer, C. S., and Spink, W. W.: J. Clin. Investigation **15**: 17, 1936.

American Academy of Pediatrics

Proceedings

SEVENTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

NEW YORK, N. Y. JUNE 3, 4 AND 5, 1937

Round Table Discussion on Sedimentation Rate

Chairman: Dr. T. Duckett Jones, Boston, Mass.
Assistants: Dr. Thomas Hale Ham, Boston, Mass.
Dr. Benedict F. Massell, Boston, Mass.

Tests for Sedimentation Rate
T. Duckett Jones, M.D.

One does not customarily consider that the practice of bloodletting, used for many centuries, was based on the same physical properties of the blood as the present day determination of the sedimentation rate of erythrocytes. Hellenic physicians conceived that health was dependent upon the normal mixture of the four fluids believed to compose the vascular contents. It was known that when a large quantity of blood was drawn from one who was ill, the blood became separated into four layers:

1. The yellowish—bile or cholera—serum which separates from the blood clot
2. A grayish-white layer called the mucus or phlegma—today called fibrin
3. Bright red blood—the sanguis or true blood—being red blood corpuscles in contact with air
4. Black bile or melancholia—dark colored substance in the lowermost portion of the clot—red blood corpuscles deprived of oxygen.

The accumulation of the phlegma was thought to be the most important cause of all disease. It was also thought that clotting of the blood depended upon coagulation of the phlegma. It was hence natural to attempt to rid the body of this "noxious agent" by venesection. Since phlegma was observed to be associated with pregnancy, this condition did not escape the drastic therapy of bloodletting.

During the 17th, 18th, and 19th centuries, the importance of the fibrinous layer was known under such names as *crusta inflammatoria, phlogistica, pleuritica, coulane du sang, buffy coat, Faserstoffhaut, speckhaut.* This altered blood was called *buffy* or *sizy,* and to Sydenham it was the pathognomonic sign of the cause of all febrile diseases, interpreted as meaning inflammation of the blood.

Paracelsus suggested that the presence of phlegma was the effect and not the cause of disease. Hewson, in 1772, recognized that corpuscles from "sizy" blood and from normal blood sink with the same rapidity in serum from normal blood, and that the sinking speed is greater in plasma than in serum from the same blood. This was the first definite suggestion that the abnormal factor is present in the blood plasma. John Hunter (1786) pointed out that in inflammatory diseases, "the red blood corpuscles become less uniformly diffused, and their attraction to one another becomes stronger." Nasse (1836) proved that the buffy coat owes

its origin to an increased sinking velocity of the red corpuscles, and that this phenomenon must have something to do with the peculiar clustering tendency of the red corpuscles. Gulliver (1845) considered the aggregation of the corpuscles as the essential property of buffy blood.

Scudamore (1826) and Andral and Gavarret (1840) found that fibrin was as a rule several times increased in sizy blood, but the fact was not associated with the increased aggregation of the red corpuscles. Muller (1833) attributed the development of the buffy coat to the quantity of fibrin. It is unquestionably true that Virchow's studies in cellular pathology diverted attention away from macroscopic studies of the blood. This must to some extent have retarded practical information to be obtained from the increased sinking velocity of the red blood corpuscles. Despite this, it was recognized by French hematologists at the beginning of this century that there was an increased aggregation of the red corpuscles in fresh blood specimens in cases of severe inflammatory conditions.

To Fahraeus[1] we are indebted for the establishment of the clinical test for the suspension stability of the blood. His work, begun in 1917, has been reported in some detail, together with a good historical summary. The original observations followed accidental observations on the increased sedimentation velocity of the red corpuscles during pregnancy. Further studies have included various phases of the subject such as the hydrodynamics of sedimentation, the causes of the increased rouleaux formation, the physicophenomena involved, and the biologic significance of reduced suspension stability.

Following the report of Westergren[2] in 1924, there have appeared thousands of reports concerning the suspension stability of the blood or the more commonly used term, the sedimentation rate of erythrocytes. Numerous methods have been devised for these determinations, resulting in a striking lack of uniformity in the interpretation of results and considerable confusion. The clinical value of the test has further been confused by the introduction of micromethods. It is our purpose to attempt to clarify some of the confusing features concerning the suspension stability of the blood and indicate the limits of the clinical value of such determinations.

When fresh venous blood is mixed with a satisfactory anticoagulant and transferred to a vertical tube, the rate of fall of the red blood corpuscles may be measured. There are three phases of fall which vary considerably, dependent upon a number of factors. Thus, a curve representing the rate of the sinking velocity of the red corpuscles is in the nature of an *S*. These three phases are as follows:

1. A period of slow sedimentation, or lag, during which the corpuscle aggregations or rouleaux form, with increasing rate of fall.
2. A period of constant fall, also the most rapid fall, which gives a true index of the sinking velocity.
3. A final period of progressive slowing during which the red corpuscles become packed.

The various factors influencing the suspension stability of the blood will be discussed later. For the present, I should like to discuss briefly the commonly used methods, especially the differences in recording of results. No micromethods will be included and many modifications of the well-established methods must be omitted for the sake of brevity. In general there are four headings under which the commonly listed sedimentation rate methods may be listed:

1. Rate of fall in millimeters per minute during the period of most rapid fall. Rourke-Ernstene[3] method.
2. Measurement of the distance which the sedimenting corpuscles fall in a specified interval of time—usually one hour. Westergren[2] and Wintrobe[4] methods.

3. Time required for the sedimenting corpuscles to fall a specified distance. Linzenmeier[5] method.

4. Graphic recording of the sedimentation of the corpuscles. Cutler[6] method.

More detailed data concerning the above methods are as follows:

Rourke-Ernstene Method.—Heparin used as anticoagulant. Hematocrit tubes graduated in 100 mm., internal diameter 4 mm. Frequent readings, at least every 5 minutes, until period of most rapid fall. Determination of fall in millimeters per minute. Correction for hematocrit. Upper limit of normal of corrected rate 0.35-0.4 mm. per minute.

Westergren Method.—3.7 per cent sodium citrate as anticoagulant in ratio of 80 blood to 20 citrate. Tubes of 300 mm. length with mark at 200 mm. mark. Internal diameter of tube 2.5 mm. Readings at 1, 2, and 24 hours. One-hour reading in millimeters usually recorded. Normal levels—men from 1 to 3 mm. with border line 4 to 7 mm. Women from 4 to 7 mm. with border line from 8 to 11 mm. Correction for hemoglobin content optional, but not used by the author of method.

Wintrobe Method.—Oxalate mixture as anticoagulant, 4 mg. potassium oxalate and 6 mg. ammonium oxalate per 5 c.c. of blood. Hematocrit tubes, graduated in 100 mm., internal diameter 3 mm. Read in one hour, recording fall in millimeters. Hematocrit correction by author's chart. Upper limit of normal 10 mm.

Linzenmeier Method.—Citrate as anticoagulant (5 per cent). Tubes 6.5 cm. in height and an internal diameter of 5 mm. Mark on tube at level of 1 c.c. and 18 mm. below this. Measure of the time required for corpuscles to fall from the 1 c.c. level to the mark 18 mm. below; 120 minutes is lower limit of normal.

Cutler Method.—Methods for 3 quantities of blood—5 c.c., 1 c.c., and 0.3 c.c. Anticoagulant 0.5 c.c. of 3 per cent sodium citrate for 5 c.c. blood. Read every five minutes for one hour and record graphically plotting fall in millimeters against time. Obtains four types of curves: (1) horizontal line; (2) diagonal line; (3) diagonal curve; (4) vertical curve. Only the horizontal line is considered normal. Upper limit of normal for the complete fall is considered 8 mm. in men and 10 mm. in women.

It may be well to mention two other variations not commonly used. Walton suggests correcting the red corpuscle quantity to a normal level prior to determining the sedimentation rate. The evident time-consuming factors here have rendered the test impractical. There is in general use in leprosy a modification of the sedimentation rate called the Rubino reaction.[7] The rate of fall of formalinized sheep cells in the serum of a patient is determined. One obvious use of the test may be mentioned, namely, the removal of the influence of fibrinogen on the suspension stability of blood. It has not been generally used to the present time.

From this brief description of commonly used tests, it is evident that many variable factors exist. It is at times confusing to determine what the report of a sedimentation rate indicates. I should like to ask Dr. Ham if he would discuss some of these variations in methods and the factors influencing the sedimentation rate of erythrocytes.

References

1. Fahraeus, R.: Acta med. Scandinav. **55**: 1, 1921.
2. Westergren, A.: Die Sankungsiektion, Ergebn. d. inn. Med. u. Kinderh. **26**: 577, 1924.
3. Rourke, M. D., and Ernstene, A. C.: J. Clin. Investigation **8**: 545, 1930.
4. Wintrobe, M. M.: Am. J. M. Sc. **185**: 58, 1933.
5. Linzenmeier, G.: München. med. Wchnschr. **70**: 1243, 1923.
6. Cutler, J. W.: Am. J. M. Sc. **183**: 643, 1932.
7. Amies, C. R.: The Rubino Reaction in Leprosy, Bull. Instit. Med. Research, Fed. Malay States, No. 4, 1929.

Critical Analysis of Method and Factors Influencing the Sedimentation Rate

Thomas Hale Ham, M.D.

A number of factors are known to cause variation in the suspension stability of erythrocytes, as measured by the sedimentation rate of the red cells in a medium of either plasma or serum.[1, 2, 5, 6, 9, 12, 18] These factors may be classified in three groups: (1) variation in the technique of measuring the sedimentation rate; (2) variation in the erythrocyte concentration and size; (3) variation in the constituents of the plasma or serum.

Variation in Technique.—The anticoagulant employed may alter materially the rate of sedimentation.[5, 6, 12, 18] If the sedimentation rate of unaltered hemophiliac blood is used as an absolute standard, then comparison can be made of the effect of any anticoagulant added to samples of the same blood.[6, 12] Solutions of sodium citrate cause significant slowing of sedimentation due to dilution and to the effect of the salt.[6] Heparin* in small concentrations has no effect,[6, 12] but in larger concentrations it produces acceleration.[6] Potassium oxalate, 20 per cent, in a concentration of 200 mg. per 100 c.c. of whole blood, has no significant effect.[6, 18] The dry mixture of ammonium and potassium oxalate introduced by Heller and Paul[7] and first used by Wintrobe for sedimentation[18] has no effect on the sedimentation rate and causes no shrinkage of the red cells.[6, 18] Decrease of the *internal diameter* of a sedimentation tube to 2.5 mm. causes significant slowing, whereas larger diameters give identical results.[6, 18] Increasing the *height of the blood column* produces progressive increase in the settling velocity of the red cells.[6, 10, 18] *Inclination of the tube* by only a few degrees from the vertical causes a sharp acceleration in the settling velocity.[10, 14, 18] The temperature of the blood is a factor, causing moderate acceleration above room temperature, and moderate retardation below.[9, 12] Prolonged *venous stasis* with shift in fluid causes alteration of the settling velocity.[11]

Variation in Erythrocytes.—Observers agree that the *concentration of erythrocytes* in suspension alters the sedimentation rate, and various methods have been devised for correction of this effect for both whole blood and defibrinated blood.[4, 5, 6, 9, 13, 14, 15, 18] *Variation in the size of erythrocytes* has been shown to alter the sedimentation velocity, macrocytes falling more rapidly than normocytes, and normocytes more rapidly than microcytes.[2, 5, 6]

Effect of Constituents of Plasma and Serum.—Many investigators have shown that the sedimentation rate correlates in a linear function with the concentration of *plasma fibrinogen.*[1, 3, 5, 6, 8, 17] In these instances the defibrinated sedimentation rate is extremely slow.[1, 5, 6] However, in instances of elevation of the concentration of *serum globulins* above 3 gm. per cent, the linear correlation of sedimentation rate and plasma fibrinogen fails completely, and the sedimentation rate of the defibrinated blood is accelerated in proportion to the concentration of the serum globulins.[1, 5, 6, 8] In some instances of *lipemia,* with elevation of cholesterol, the sedimentation rate of whole blood may fail to correlate with the plasma fibrinogen content, and the rate of the defibrinated blood may be extremely elevated in spite of normal or decreased concentrations of serum globulins.[5, 6]

Methods of Measuring the Sedimentation Rate.—A great variety of methods has confused the literature and prevented comparison of results: The various techniques differ in the following respects: (1) anticoagulant type, concentration and dilution; (2) tube diameter; (3) height of the blood column; (4) correction for anemia; (5) method of timing the sedimentation rate; and (6) units employed in recording the results. As already mentioned, each of the first four factors may influence the rate materially. Since the sedimentation of erythrocytes always produces an *S* shaped curve, as already described by Dr. Jones, the method of timing the rate must be chosen accordingly. The only comparable portions of any

*Hinson, Westcott and Dunning.

two sedimentation curves are the slopes or rates of the respective periods of constant fall.[6, 10, 13] Therefore, other methods of timing fail to measure similar portions of a variety of curves. Using the slope or tangent method of measuring

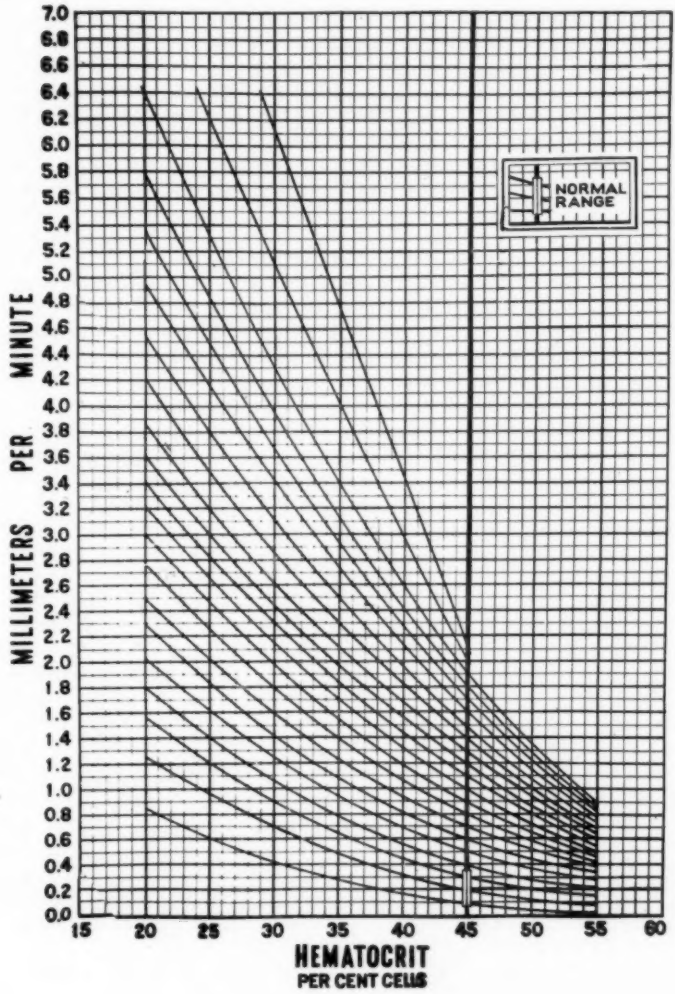

Fig. 1.

the rate, the Rourke-Ernstene technique[13] produces a more linear correlation with plasma fibrinogen concentrations than the procedures of Wintrobe[18] and Westergren.[9, 16]

Method of Choice.—If a linear correlation between sedimentation rate and plasma fibrinogen concentration is the criterion for selection of a sedimentation technique, the method of choice is that of Rourke and Ernstene.[13] The technique is performed as described by the authors, using heparin as anticoagulant. As shown by Win-

trobe,[18] a dry mixture of ammonium and potassium oxalate can be substituted for heparin. In repeating the experiments of Wintrobe[18] and of Rourke and Plass,[12] this fact was corroborated: the dry oxalate mixture* caused no alteration of sedimentation rate or hematocrit when added to hemophiliac blood and compared to an unaltered sample of the same blood. It was necessary, however, to observe the sedimentation within two hours of obtaining the blood sample, since three hours' standing frequently produced significant slowing of the rate.[6, 18] Using heparin, no slowing was observed as a result of six hours of standing at room temperature. Employing either heparin or dry oxalate mixture as anticoagulant, the Rourke-Ernstene method includes the following features which distinguish it from other techniques: (1) an anticoagulant which does not alter the sedimentation rate or hematocrit; (2) a tube which does not retard the rate, and which is employed to determine the cell volume, or hematocrit; (3) the slope, or tangent method of timing; (4) a hematocrit correction which is satisfactory; (5) a more linear correlation with plasma fibrinogen than similar methods.[5, 6]

Significance and Limitations of the Sedimentation Rate.—Since the sedimentation rate, which measures the degree of suspension stability of the erythrocytes, is influenced by a variety of factors, it must be classified as a nonspecific phenomenon. For example, an elevated whole blood sedimentation rate may be associated with abnormal concentrations of plasma fibrinogen, or elevated serum globulins, or with both. It is possible, by knowledge of the corrected defibrinated sedimentation rate, to predict whether an elevated whole blood rate will correlate in a linear manner with fibrinogen concentrations.[5, 6] However, the clinical interpretation of any sedimentation rate depends only upon the significance of the blood constituent which is abnormal. Therefore, the sedimentation test has clinical value only as an indirect method for estimating the concentration of blood variables such as plasma fibrinogen, serum globulins, and lipoids. As employed in clinical medicine it usually serves as a rough estimate of the plasma fibrinogen, which has significant variations in health and disease.[5, 6] The causes of fibrinogen variations differ widely from the causes of variations in the other globulins and in lipoids. The sedimentation rate of neither whole blood nor defibrinated blood can serve as an accurate method for determining the concentration of any blood constituent.[5, 6] Thus the corrected sedimentation rate of whole blood must be considered as a nonspecific test, usually giving a rough estimate of the fibrinogen concentration, but unreliable as a specific or accurate quantitative procedure. Similarly, the corrected defibrinated sedimentation rate is nonspecific, giving an estimate of the concentration of either serum globulins or lipoids, but failing as a specific or accurate quantitative procedure.[5, 6]

References

1. Bendien, W. M., and Snapper, I.: Biochem. Ztschr. **235:** 10, 1931.
2. Bendien, W. M., Neuberg, J., and Snapper, I.: Biochem. Ztschr. **247:** 306, 1932.
3. Gilligan, D. R., and Ernstene, A. Carlton: Am. J. M. Sc. **187:** 552, 1934.
4. Gram, J. D.: Acta med. Scandinav. **68:** 108, 1928.
5. Ham, Thomas Hale: J. Clin. Investigation **15:** 470, 1936.
6. Ham, Thomas Hale: In Press.
7. Heller, V. G., and Paul, Henry: J. Lab. & Clin. Med. **19:** 777, 1934.
8. Kylin, E.: Acta med. Scandinav. **85:** 574, 1935.

*The oxalate mixture used in these experiments was prepared as follows: 3 gm. of crystalline ammonium oxalate and 2 gm. of crystalline potassium oxalate were dissolved in distilled water with the aid of heat, and diluted to a final volume of 100 c.c. This gave an oxalate mixture concentration of 5 per cent and a ratio of 60 per cent ammonium to 40 per cent potassium oxalate. The concentration employed was 200 mg. of oxalate mixture in 100 c.c. of whole blood. Therefore, for each cubic centimeter of blood drawn, 0.04 c.c. of the anticoagulant was required. For routine work, Wassermann tubes were calibrated by a diamond scratch at a 2 c.c. volume. Then 0.08 c.c. of the solution of oxalates was pipetted into each tube, and the anticoagulant completely dried in an oven at 100°C. for one half hour, or left for several days in a desiccator at room temperature. A large number of these tubes were prepared at one time and stored.

9. Leffkowitz, Max: Handbuch d. Allgemeinen Hamatologie, Band 2, erste Halfte, p. 435, Urban and Schwarzenberg, 1933.
10. Lundgren, R.: Acta med. Scandinav. **67**: 63, 1927.
11. Plass, E. D., and Rourke, M. D.: J. Lab. & Clin. Med. **12**: 735, 1927.
12. Rourke, M. Dorothy, and Plass, E. D.: J. Clin. Investigation **7**: 365, 1929.
13. Rourke, M. Dorothy, and Ernstene, A. Carlton: J. Clin. Investigation **7**: 545, 1930.
14. Walton, A. C. R.: J. Lab. & Clin. Med. **18**: 711, 1933.
15. Westergren, Alf: Ergebn. d. inn. Med. u. Kinderh. **26**: 577, 1924.
16. Westergren, Alf: Am. Rev. Tuberc. **14**: 94, 1926.
17. Westergren, Alf, Theorell, Hugo, and Widstrom, Gusta: Ztschr. f. d. ges. exper. Med. **75**: 668, 1931.
18. Wintrobe, M. M., and Landsberg, J. W.: Am. J. M. Sc. **189**: 102, 1935.

Clinical Application of the Sedimentation Rate

B. F. Massell, M.D.

Dr. Jones and Dr. Ham have presented a brief history of the sedimentation rate, an analysis of the factors responsible for changes in the suspension stability of the red blood cells, and a critique of the various methods of performing the test. We may now turn to a consideration of the clinical application of the sedimentation rate. The physician is interested chiefly in knowing whether the test can aid him in the diagnosis and treatment of his patients. If it has such practical potentialities, he wants to have sufficient knowledge of the facts about it to allow for intelligent usage and critical interpretation. It is the purpose of this paper to present as briefly as possible those facts which are known.

The sedimentation rate is a nonspecific reaction. It may be accelerated by almost any process which causes increased tissue breakdown or injury, whether this process be infectious, toxic, metabolic, neoplastic, or mechanical. Numerous papers, already adequately reviewed[1, 2] have been written about the sedimentation rate showing that it may be elevated in tuberculosis, rheumatic fever, and various types of acute arthritis, pelvic inflammation, active acquired and congenital syphilis, all acute infectious diseases including the exanthemas, acute suppurative processes such as otitis media, mastoiditis, sinusitis and osteomyelitis, acute pulmonary conditions including pneumonia, pleurisy, infarct and abscess, myocardial infarction, a variety of tropical diseases such as kala-azar and malaria, nephritis, carcinoma, and other malignancies, fractures and aseptic wounds, burns, lead and arsenic poisoning, and thyrotoxicosis. Because of this great variety of conditions which may alter the sedimentation rate, it is apparent that the test usually does not help to differentiate one disease process from another.

Likewise, the test has no diagnostic value in the study of patients who have definite fever or frank leucocytosis, or present other adequate signs of pathology. In such instances it will provide nothing but unnecessary confirmatory evidence.

The sedimentation rate's chief virtue is its sensitivity, whereby it may detect the presence of a disease process in the absence of all other signs. Therefore, the sedimentation rate is a test worth doing along with other tests and procedures in the routine check-up of patients in the hospital, office, or clinic. An abnormal sedimentation rate, even in the presence of negative findings by physical examination and other laboratory procedures, should be viewed with suspicion and a diligent search should be made for its cause. Cutler,[3] among others, has emphasized the use of the sedimentation rate as part of the routine examination. Of 1,000 patients on whom this test was performed, he found 328 who were "apparently healthy" or who had "trivial disturbances." Of these, 177 (54 per cent) had abnormal sedimentation rates. Careful studies on these 177 patients revealed 96 with basal, nontuberculous infiltration of the lungs, 32 with latent tuberculosis of the apices, 35 with a positive Wassermann reaction, 5 with pelvic inflammatory disease, and one with carcinoma of the lung.

In the differentiation of organic and functional conditions, the sedimentation rate may be helpful. It is not infrequent that patients present symptoms which are vague and which are unassociated with any abnormal physical signs, and in such circumstances the sedimentation rate may be a valuable lead. In instances where a neurosis is suspected as the cause of symptoms, the finding of a normal sedimentation rate would be confirmatory of a psychogenic background, while the finding of a rapid sedimentation rate would suggest an organic origin.

Again because of its sensitivity, the sedimentation rate has proved to be especially valuable as a guide to the treatment of patients ill with chronic diseases. This is particularly true of tuberculosis and rheumatic fever. Since there is no specific therapy for either of these conditions, long bed rest is the chief weapon which the physician has, and it is generally accepted that rest should continue until the infection has completely subsided. After the acute manifestations of these diseases have regressed and finally disappeared, the sedimentation rate frequently remains elevated for weeks to many months. Such an abnormal sedimentation rate in a tuberculous or rheumatic subject, in the absence of other possible causes, should be considered as evidence of persistent active tuberculosis or rheumatic fever.

Many investigators who have written about the sedimentation rate in these conditions have claimed for it a remarkable infallibility. They have either implied or stated directly that an elevated sedimentation rate proves the presence of active infection and that a normal sedimentation rate proves the absence of active infection. If the word "suggests" were substituted for "proves" this statement would be more nearly correct. The value of the sedimentation rate as an adjunct in following the course of chronic diseases cannot be denied, and its use is highly recommended, but other laboratory tests such as the leucocyte count and the evaluation of the clinical status of the patient must not be neglected.

Thus Banyai and Anderson[4] in a study of 2,000 cases of tuberculosis found 7.3 per cent with a normal sedimentation rate. This group with a normal sedimentation rate included 14 with minimal pulmonary tuberculosis, 54 with moderately advanced tuberculosis, 13 with advanced tuberculosis, and 47 with extrapulmonary tuberculosis. The last group with coexisting active extrapulmonary tuberculosis and a normal sedimentation rate included 19 children with hilar tuberculosis, 6 cases of tuberculous pleurisy, 1 case of tuberculous peritonitis, and 8 cases of tuberculous lymphadenitis.

Similarly, in a study[5] of 178 rheumatic fever patients it has been shown that, although the sedimentation rate frequently indicated the presence of active infection after the subsidence of all clinical manifestations and in the presence of a normal leucocyte count, the reverse also was often true. There were many cases in which the leucocyte count remained elevated for a varying period after the sedimentation rate had returned to normal and there were some instances in which there were definite clinical manifestations of rheumatic fever in the presence of a normal sedimentation rate. The chief clinical signs of rheumatic fever which were sometimes present singly or in combination in spite of normal sedimentation rate were epistaxis, erythema marginata rash, subcutaneous nodules, and a slightly elevated rectal temperature. Patients with chorea but no other manifestations of rheumatic fever frequently had normal sedimentation rates, although in an equal number the test was elevated.

In connection with this discussion of the leucocyte count and sedimentation rate in detecting low-grade rheumatic fever, it should be pointed out that in view of the large percentage of error in the technique of the leucocyte count and therefore the necessity for repeated counts, the sedimentation rate is more valuable as a single isolated test.

Because of its sensitivity, the interpretation of an elevated sedimentation rate must be made with caution. It must be remembered that it may be affected by almost any type of bodily disturbance. Such relatively minor conditions as ton-

sillitis or tonsillectomy will cause the sedimentation rate to become elevated, and a normal level may not be reached for two to four weeks. Cervical adenitis or other complications may cause the elevated sedimentation rate to continue even longer. Therefore, following an upper respiratory infection or operation in a tuberculous or rheumatic subject an interval of four weeks should elapse before interpreting an abnormal sedimentation rate as indicative of active tuberculosis or rheumatic infection.

Early in the course of acute pathologic conditions the finding of a normal sedimentation rate should not cause surprise, for the response of the sedimentation rate is not rapid and definitely lags behind the temperature and leucocyte count. It may not become elevated for six to twenty-four hours after a rise in temperature, and a maximum level may not be reached for several days. For this reason it is often normal during the first twenty-four hours of an attack of acute appendicitis. Therefore, the finding of a normal sedimentation rate in a patient suspected of acute appendicitis or similar episode of short duration may be misleading if this fact is not fully realized. The association of a normal sedimentation rate with early appendicitis has been utilized in the differentiation of this condition from gonorrheal salpingitis in adult women. In the latter the acute episode has usually been preceded by previous gonorrheal infection so that the sedimentation rate is likely to be already elevated at the onset of the more acute attack.

The sedimentation rate in addition to its sensitivity to mild or latent pathological changes has the virtue of being affected by very few physiologic conditions. Pregnancy is the only definite exception. After the tenth to twelfth week the sedimentation rate rises and it may remain elevated as late as four weeks postpartum. The catamenia has at the most an insignificant effect, while ingestion of food and short, vigorous exercise do not alter the test. A consistently elevated sedimentation rate has been observed in several obese individuals, apparently without discoverable cause. This suggests that obesity may sometimes increase the sedimentation rate, but the acceptance of this as a fact must await adequate investigation. During infancy the sedimentation rate is said to be normally very slow, but for children and adolescents the normal range is the same as for adults.

Although the sedimentation rate is increased by a great variety of conditions, there are certain abnormal bodily states in which it is not likely to be elevated. A normal or even subnormal rate is usually associated with hay fever, asthma, and other allergic conditions uncomplicated by infection. Extremely low-grade infections such as mild dental infections, chronic tonsillitis and chronic nonsuppurative sinusitis usually do not cause an elevated sedimentation rate, but this is not a constant finding. Disease of the liver and biliary tract, as of any other organ of the body, may increase the sedimentation rate, but sometimes normal rates are associated. The latter is particularly apt to be true when there is liver damage. The cause for this has not been determined, but it may be related to a decreased fibrinogen production by a poorly functioning liver, or to the presence in the plasma of bile salts which tend to increase the suspension stability of the red blood cells.

Associated with the development of congestive failure in patients ill with rheumatic fever, previously elevated sedimentation rates usually become lower and may fall to within normal limits. Therefore, in patients with congestive failure the finding of a normal sedimentation rate cannot be considered as evidence against the presence of active infection. The mechanism for the slowing of the sedimentation rate by congestive failure is not known but possibly may be indirect through the effect of the latter on the liver.

The sedimentation rate is said to be usually normal in coxa plana and that therefore it is of value of differentiating this condition from tuberculosis of the hip.

Finally, emphasis must be given to the obvious fact that the more accurate the method chosen for determining the sedimentation rate, the more reliable is its

interpretation. It already has been conclusively shown that variations in red blood cell volume greatly affect the sedimentation rate so that methods not involving a correction for this factor are not accurate. Of those methods which do correct for this factor, that described by Rourke and Ernstene[6] is one of the most satisfactory.

References

1. Wintrobe, M. M.: Internat. Clin. **2**: 34, 1936.
2. Walton, A. C. R.: Quart. J. Med. **2**: 79, 1933.
3. Cutler, S. W.: Am. J. M. Sc. **183**: 643, 1932.
4. Banyai, A. L., and Anderson, S. V.: Arch. Int. Med. **46**: 787, 1930.
5. Massell, B. F., and Jones, T. D.: New England J. Med. **215**: 1269, 1936.
6. Rourke, M. D., and Ernstene, A. C.: J. Clin. Investigation **8**: 545, 1930.

DISCUSSION

DR. CARL H. SMITH (NEW YORK CITY).—Dr. Ham is to be congratulated on his presentation of fundamental studies in which the various factors controlling the rate of erythrocyte sedimentation have been analyzed. He has pointed out clearly the close correlation existing between the fibrinogen content and the cell volume with the change in the suspension stability of the blood.

The method of Rourke and Ernstene which was employed in these studies, incorporates the most desirable refinements of the technique. Yet, in the hands of the pediatrician, it may, in common with other methods, present several drawbacks. Since the essential significance of the sedimentation reaction rests on the results of successive determinations, blood specimens must be readily obtainable. In dealing with infants and children, practical difficulties often arise from the necessity of finding suitable veins for repeated punctures and from the undesirable effects of the attendant anxiety of the patient. With younger children particularly, a method is preferable which utilizes capillary blood, and in which the tube employed embodies the basic specifications and features of a standard venipuncture method. If possible, the results obtained should approximate those with venous blood methods. My experience during the last three years with such a sedimentation tube has been entirely satisfactory.

The procedure of determining the "corrected sedimentation index" is often beyond the scope of the practitioner; since readings must be made at short intervals, the period of constant sedimentation must be isolated, the curve plotted, and correction made for the factor of anemia. Where the facilities are available, such procedure is most desirable. The value of sedimentation rates, however, is derived not from a single determination, but by noting the trend of successive readings. Such information may be readily obtained by comparing the readings at the end of a fixed time interval with the use of other reliable and less time-consuming procedures.

In the evaluation of the sedimentation test, the influence of the concentration of hemoglobin, erythrocytes, and cell volume percentage upon the sedimentation rate has been repeatedly emphasized. That an inverse ratio exists between the rate of settling of the cells and their number has been pointed out by many investigators. The factor of anemia is important since the test is designed to indicate solely the degree of existing infection and tissue damage. While it is doubtless true that correction for concentration and volume percentages of erythrocytes is justified, several difficulties are again encountered. First, methods for correction are usually not interchangeable because of lack of uniformity of sedimentation tubes and technique. A correction curve has, therefore, to be prepared for each sedimentation method. Second, with both the Rourke and Ernstene and the Wintrobe methods, the rate is corrected in terms of a standard volume of packed cells. These values range, however, above those obtained for children, particularly of the younger age

groups, as recently determined by Osgood and Baker and by Mugrage and Andresen. It would be necessary, with children, to transpose the rates in accordance with values corresponding to specified age levels. To obviate some of these difficulties, a practical plan would be simply to report the hematocrit reading with the sedimentation rate as determined directly from the tube. The results should then be interpreted in accordance with the degree to which the cell volume percentage approximates the normal for the age.

A word may be said concerning the peculiar behavior of anemic blood during sedimentation. Curves for correction of sedimentation rates are constructed usually from samples of diluted blood. Fahraeus was one of the first to point out, however, that the blood in anemia does not sink as rapidly as one would expect from dilution experiments. In studies now in progress, I have found instances of children suffering from nutritional anemia whose hematocrit values were below normal, yet whose erythrocytes sedimented very slowly. In a study with the blood of experimental anemia in rabbits, Gregg similarly observed that during some of its phases suspensions of red cells from the anemic animal sedimented very slowly. Anemia may, therefore, represent more than a simple reduction of the red cells accompanying infection. Its effect upon the rate of sedimentation is probably a resultant of diverse forces depending upon the etiology of the anemia.

DR. HENRY P. WRIGHT (MONTREAL, QUE.).—In using the Wintrobe method every two months in tuberculous children, I find that the influence of emotion seems, in some instances, to elevate the rate. At a subsequent time with the child tranquil, the rate drops. Is there any correlation between the Mantoux reaction and sedimentation rate?

DR. MASSELL.—To my knowledge there has been no definite study of the influence of emotion upon the sedimentation rate. I know of one report in which it is stated that the sedimentation rate of children was higher on the day of admission to a hospital than it was several days or weeks later. The emotional upset associated with being sent to a hospital was thought to be a factor in the production of the initial elevated rate. That emotion does not affect the sedimentation rate is suggested by the fact that patients ill with functional psychoses usually have a normal sedimentation rate.

The sedimentation rate and the Mantoux reaction show no definite correlation. In the presence of a positive Mantoux reaction an elevated sedimentation rate would suggest active tuberculosis, whereas a normal sedimentation rate would suggest a quiescent or latent lesion. The effect of the tuberculin test itself on the sedimentation rate is said to be of value in the diagnoses of active tuberculosis. Following the tuberculin test, the sedimentation rate is more likely to become accelerated if there is active tuberculosis than if there is no tuberculosis or quiescent tuberculosis.

CHAIRMAN JONES.—I have seen both normal and abnormal sedimentation rates in children who had a violent emotional reaction during the taking of blood. In none of these, however, has there been a repetition of the test to determine the possible effect of the emotional factor.

DR. ALFRED G. LANGMANN (NEW YORK CITY).—Is the sedimentation rate elevated in pure chorea? If a child requires tonsillectomy, do you wait for a normal sedimentation rate before operation?

CHAIRMAN JONES.—We would not consider a case as being straight, simple chorea if any laboratory work such as leucocyte elevation, sedimentation rate or prolongation of the P-R interval by electrocardiogram, or clinical manifestation points to rheumatic fever. In the presence of any of the above enumerated findings, the patient is treated as a rheumatic fever subject, with chorea as one of the clinical manifestations. We make it a rule to do tonsillectomies only when there is no

evidence of active rheumatic fever. Hence, an abnormal sedimentation rate would make us postpone the procedure. In following this rule, we have had very few post-tonsillectomy rheumatic fever recurrences.

DR. EDWARD P. BAGG (HOLYOKE, MASS.).—What do you consider the significance of a fast sedimentation rate in the patient with a normal electrocardiogram?

CHAIRMAN JONES.—I should consider the fast sedimentation rate an indication of low-grade rheumatic fever. In chronic rheumatic fever evidence of activity, obtainable by electrocardiogram, occurs in only 20 to 25 per cent of the cases.

DR. H. C. THOMPSON, JR. (ALBANY, N. Y.).—Would it not be as good, in determining sedimentation rate to make a correction for the total number of cells as to make a correction by means of the hematocrit?

DR. HAM.—I have been interested in this question because not every one has the centrifuge necessary for hematocrit work. It is unquestionably best to correct for hematocrit, though I believe an index might be arrived at to correlate both the red blood cell count and the hematocrit.

DR. THOMPSON.—Does the sedimentation rate become altered and remain rapid for two or three weeks after tonsillectomy in normal as well as in rheumatic children?

DR. MASSELL.—Tonsillectomy in normal individuals as well as in rheumatic patients may cause the sedimentation rate to become accelerated. In fact, any aseptic operation (such as a herniotomy) or severe injury (such as bone fractures) may cause an increase in the sedimentation rate for one to three weeks.

DR. B. FEINBERG (PROVIDENCE, R. I.).—Can an accurate graph be determined from blood obtained by skin puncture? Does the average laboratory, when reporting the sedimentation rate, give the corrected rate?

DR. HAM.—I have had no experience with the Cutler method or other micromethd because I have felt that small tubes introduced factors of error. As to the question of whether the usual laboratory reports the corrected rate, I should say that it does not. As far as I know, there has never been a corrected figure for anemia in the Linzenmeier method. I realize I have to be very careful in answering this question specifically. Certain laboratories have no centrifuge for the hematocrit correction. As a whole, the Cutler, Linzenmeier, and other methods give you what you want. That is to say they are utilitarian but not academic, and will occasionally fool you. I have been most interested in the academic side.

CHAIRMAN JONES.—Am I correct, Dr. Ham, in assuming that no correction is made for cell volume unless so stated in the laboratory report on the hospital chart? Also, what method is indicated when the sedimentation rate is reported in four separate millimeter readings, such as 4– 8– 12– 16? This seems commonly used but is not one of the standard methods we have discussed today.

DR. HAM.—In general, I would say that every author or institution develops some modification of the original methods, becoming familiar with its own modification and technique. It is sometimes extremely difficult, in reading the literature, to correlate these modifications.

DR. WRIGHT.—What is the accuracy of the red blood count compared to that of the hematocrit? Is there any correlation?

DR. HAM.—As I mentioned, I attempted to do various things to check possible sources of error, and I rely upon the hematocrit above the red blood cell count or hemoglobin estimate.

CHAIRMAN JONES.—That is an important point.

DR. R. V. NICHOLAS (PHILADELPHIA, PA.).—What does a normal sedimentation rate indicate in a syphilitic patient who has had positive Wassermann and Kahn tests, and whose sedimentation rate was previously rapid?

DR. MASSELL.—It probably means that the syphilitic process has become less active. However, the correlation of the sedimentation rate with the activity of the syphilitic infection is not sufficiently dependable to utilize it as a guide to determine the cessation of treatment.

DR. L. C. ROSENBERG (NEWARK, N. J.).—Will Dr. Ham please discuss the value of, and compare, heparin and the potassium and ammonium oxalate mixture as anticoagulants? Will Dr. Ham review the technique of the Rourke-Ernstene method of sedimentation rate?

DR. HAM.—In answering this question, I described the Rourke-Ernstene technique, stressing the influence of temperature and method of drying. Heparin is very expensive, and the potassium ammonium oxalate can easily be substituted for it as shown by Wintrobe. The dry oxalate mixture causes no alteration of sedimentation rate or hematocrit when added to hemophiliac blood and compared to an unaltered sample of the same blood.

DR. LEWIS ROBBIN (NEWARK, N. J.).—In view of the difficulties and uncertainties, I consider the sedimentation rate as secondary to clinical judgment.

CHAIRMAN JONES.—I agree heartily and would not want to get away from the importance of clinical judgment. Dr. Massell has pointed out that the sedimentation rate is an unnecessary procedure in an obviously ill patient. However, a fast sedimentation rate, if repeated, must be considered as being significant. In two instances, we have seen abundant pathologic evidence of active rheumatic fever in which the sedimentation rate was practically the only evidence of the active disease. Both of these patients died very suddenly after seeming to be clinically well, and there was not time for the pathologic changes to have developed as a result of the terminal difficulty.

DR. M. L. BLATT (CHICAGO, ILL.).—What is the relationship between blood viscosity, carbon dioxide tension and sedimentation rate?

DR. HAM.—The viscosity of whole blood increases in proportion to the erythrocyte concentration and the sedimentation rate decreases as the whole blood viscosity rises. No direct causal relationship has been demonstrated, however, between viscosity and the sedimentation rate. An increased carbon dioxide tension has been observed to cause swelling of the erythrocytes, an increase in the cell volume percentage of erythrocytes and a slowing of the sedimentation rate.

DR. HERMAN SCHWARZ (NEW YORK CITY).—What is the relationship between the blood salts and sedimentation rate?

DR. HAM.—An increase in the sodium chloride content of the whole blood, by in vitro addition causes a slowing of the sedimentation rate as shown by Ennockson.

DR. E. H. NICKMAN (ATLANTIC CITY, N. J.).—Have any studies been made comparing the nuclear index of leucocytes and sedimentation rates as an index of abnormal processes?

DR. MASSELL.—Yes, such studies have been reported and in most instances the sedimentation rate was said to be more sensitive and, therefore, superior to the nuclear index. Although we have had no personal experience with the nuclear index, we nevertheless suspect that there are many cases in which the nuclear index may reveal the presence of an abnormal process in the presence of a normal sedimentation rate.

DR. L. T. ROYSTER (UNIVERSITY, VA.).—In the course of quiescent rheumatic fever, why does tonsillectomy affect the rate?

CHAIRMAN JONES.—The fast sedimentation rate following tonsillectomy is not peculiar to quiescent rheumatic fever but occurs even in normal subjects. It is probably due to the fibrinogen content of the blood.

DR. MORRIS GREENBERG (NEW YORK CITY).—Do you find sedimentation rate changed in chorea?

CHAIRMAN JONES.—In simple chorea the sedimentation rate is often or usually normal. In chorea patients with other manifestations of rheumatic fever, a past history of rheumatic fever, or rheumatic heart disease it is often fast.

DR. I. PALMIERI (BROOKLYN, N. Y.).—Why is the sedimentation rate very slow in infants?

DR. MASSELL.—The sedimentation rate is said to be slow in newborn infants and that it gradually increases toward normal as the infant grows older. An opinion has been expressed that this relatively slow sedimentation rate in infancy is due to a low blood fibrinogen. However, most of the methods used in these studies of the sedimentation rate in infancy have not involved a correction for variations in the red cell volume, and it is possible that another factor is the relatively high red cell volume which is present in the newborn.

DR. PALMIERI.—Is there any difference between capillary blood and venous blood in the determination of sedimentation rate?

DR. HAM.—This question has been answered in response to the discussion by Dr. Carl H. Smith.

DR. MOORE (CINCINNATI, OHIO).—What is your experience with sedimentation rate in the diagnosis of early whooping cough?

DR. MASSELL.—We have had no personal experience with the sedimentation rate in whooping cough. However, other investigators have reported a definite retardation of the rate of fall of the red cells in patients ill with this disease and therefore have offered it as another procedure to be used as an aid in the differentiation of whooping cough from other types of respiratory infection in which the sedimentation rate is usually accelerated. To my knowledge the cause for this slow sedimentation rate in whooping cough is not known.

DR. HAM (in answer to Dr. Carl H. Smith).—A number of investigators have shown that the sedimentation rate of citrated blood is the same from the following three sources: arteries, veins, and capillaries. There is no doubt that much valuable information may be obtained from a microsedimentation technique using capillary blood, as discussed by Dr. Smith. Much of the confusion which exists in the discussion of various methods could be avoided if each technique were standardized as follows: Determine the degree of accuracy with which any given technique will measure the concentration of plasma fibrinogen. Although other factors than fibrinogen will play some rôle, the sedimentation test has its major value as an indirect method for estimating the concentration of plasma fibrinogen.

CHAIRMAN JONES.—I should like to thank all discussers and those who asked questions. I hope that we have helped clarify some of the confusion concerning the methods, as well as reviewing the factors which influence the suspension stability of the blood corpuscles. It may be well to repeat that the sedimentation rate is of the most value as a guide to the course of chronic diseases, such as tuberculosis and rheumatic fever. It may also help considerably in determining that there is actual disease present in some of the difficult diagnostic problems. I thank you for your long sustained attention during this discussion.

SEVENTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

NEW YORK, N. Y., JUNE 3, 4, AND 5, 1937

Panel Discussion on Present Status of Active Immunization Against Scarlet Fever

CHAIRMAN: DR. RALPH S. MUCKENFUSS, NEW YORK, N. Y.
ASSISTANTS: DR. JEAN V. COOKE, ST. LOUIS, MO.
DR. A. R. DOCHEZ, NEW YORK, N. Y.
DR. PAUL S. RHOADS, CHICAGO, ILL.
DR. PHILIP M. STIMSON, NEW YORK, N. Y.
DR. WILLIAM THALHIMER, NEW YORK, N. Y.

DR. PHILIP M. STIMSON.—The problems of scarlet fever which are most important are: Shall we immunize our patients against this infection? Have we a satisfactory method of changing a positive Dick reaction without undue discomfort or trouble to the patient? Is making a person Dick-negative worth while? Is scarlet fever still sufficiently dangerous to make us want to immunize all children and, on the other hand, have we reliable enough remedies to warrant promising our patients a satisfactory recovery? Should they take their chances and let a positive Dick test stay positive? What is the entire significance of a positive Dick test anyhow?

I am not going to try to answer all those questions by any manner of means. I am throwing into the pot some ideas about which my confreres know a great deal more than I, and I present these thoughts to them to discuss.

Scarlet fever is not as serious as it used to be. In New York City the case death rate has dropped so that now it is estimated only six children die out of every thousand patients with scarlet fever; whereas fifteen years ago the figures were about six times as much.

On the other hand, the number of cases occurring each year has not diminished appreciably since the beginning of the century. The years 1908 and 1932 have been the high years in New York City for this century. The lowest half decade was that of the War, 1916 to 1920.

In hospitals, also, the mortality has diminished. In Willard Parker the mortality is only 1.1 per cent. But, on the other hand, an eighth of all hospital cases of scarlet fever develop or have developed before admission purulent otitis media with its menace of mastoiditis and ensuing loss of hearing.

Scarlet fever is not particularly contagious. In a contagious disease hospital we do not have trouble with scarlet cross-infections, that is, patients with other illnesses catching scarlet fever. In approximately ten thousand admissions with other diseases during the past five years in the Willard Parker Hospital, there were only sixteen ward infections with scarlet fever, an eighth of one per cent, although nothing was done to immunize the ward patients with scarlet fever.

However, of 1,300 pupil nurses sent to us for three months' training in contagious diseases during the past five years, all supposedly Dick negative before arrival in our hospital, thirty-four or about 2.5 per cent developed scarlet fever in the three-month course at the hospital. Since January 1 of this year, however, we have done our own Dick tests and as yet have had no infections among some two hundred pupil nurses, because those we found with positive Dick tests have not been allowed to go near patients with scarlet fever.

A patient with scarlet fever, as it usually occurs these days, is sick less than a week, and the mothers say it is not much of a disease; but, on the other hand, the average hospital stay is twenty-three days at the present time. So, even if they are not very sick, they are confined a long time. There is also an economic factor, that is, the cost to the city for the care of these hospital patients.

There are various explanations why scarlet fever is apparently becoming more mild. One is that the disease is becoming less virulent because the worst cases are isolated, allowing the virulent strains to die out because of isolation. On the other hand, patients suffering from infections due to mild strains are often not isolated because the true nature of their illness is not recognized, and such patients pass along their streptococci. This is a survival of the weakest as it were.

The recognition of long periods of mild scarlet fever is not new. Trousseau, at the beginning of the last century, stated that in thirty years' practice he had never seen a fatal case of scarlet fever. The next winter there was a small epidemic in which a third of the patients died. Today, a virulent form of scarlet fever exists in the Balkans, and every now and then a severe case appears here in New York City, although for some fifty years statistics show there has been a fairly steady decline in mortality rates in most countries. A severe epidemic may burst out again at any time due to factors beyond our present knowledge.

Many statistics have been published showing that by giving inoculations enough to render everyone Dick-negative, scarlet fever has been essentially wiped out in large groups of people—nurses in training, children in institutions, and so forth. Yet it is well known that Dick-negative individuals are susceptible to throat and other infections with scarlatinal streptococci, which are usually not recognized as such. They, therefore, are often not well isolated and constitute fertile sources of dissemination of the scarlatinal streptococci, especially to new contacts.

The immunity acquired after infection with one strain of scarlatinal streptococci may have a very limited specificity and may afford protection against reinfection by that particular strain only, or possibly only a small number of the twenty-seven strains that Griffith, in England, has now identified. *The Journal of Hygiene*, Volume 37, p. 153, 1937, reports that 70 per cent of the scarlet fever patients in a multiple bed ward picked up new strains from their neighbors and that a majority of the complications occurring during the third week and after were due to these new infections, as were also all of ten so-called relapses. All of these ten relapses studied were due to different strains of scarlatinal streptococci from that which caused the primary case of scarlet fever.

The Dick reaction, we know, is altered by various nonspecific factors. Debre has shown that the Dick test is often made negative in various of the contagious diseases, notably measles. On the other hand, vaccination has been found at times to have an augmenting influence on the Dick test.

The skin reaction to the toxin is certainly interesting and subject to much variation and interpretation. I have with me a picture which unfortunately can be seen only by those at the table. It is a colored plate of a very heavy rash on a girl who had had at the wrist a pre-existing infection which had healed shortly before scarlet fever developed. When the scarlet rash appeared, it did not affect the area of the skin at the site of the small infection nor along the lymph channel up to the epitrochlear node at the elbow, having a white area and pathway where the rash never appeared.

Then, also, there are photographs here of a very heavy eruption on the body of a woman who had scarlet fever this past March, the eruption being quite sharply and clearly bounded by the limits of her one-piece bathing suit which she had

worn eight months before while getting very well tanned. Only the untanned skin showed the eruption. I confess to considerable uncertainty in explaining these two conditions. Are they due to nonspecific states of tissue exhaustion or augmentation, or is there local tissue hyposensitization?

My own belief regarding scarlet fever immunization has been that everybody who has to do with scarlet fever patients—nurses, doctors, attendants and members of the immediate family of a given patient—should be made Dick-negative, whatever its significance may be. This may be done with injections of toxin if enough are given, but I believe in a very small initial dose, as has recently been advocated by Rappaport. Instead of the toxin, an injection of convalescent serum is used where only temporary protection is necessary.

DR. THALHIMER.—Apparently there are large numbers of individuals who are susceptible to scarlet fever and also a very large number of individuals, too, who contract this disease. It would appear there is a field of usefulness for means of passive immunization of some of these individuals against single exposures to this disease and for the treatment of individuals who actually have contracted it.

In recent years my interest has been mainly in the convalescent serum field. By convalescent scarlet fever serum we mean a human serum which has been prepared by pooling the serum obtained from blood secured from about thirty individuals recently recovered from the disease and at two- or three-week intervals up to a period of four months after onset of the disease. This serum must be very carefully and gently handled so as to avoid hemolysis, and, of course, it must be negative to Wassermann and precipitation tests and must fulfill all the requirements of sterility.

The importance and usefulness of various convalescent serums have been demonstrated wherever sufficient serums have been made available. It seems to me after considerable experience of my own and after the experience of many others that properly prepared human serum is about as bland a material as is available for injection subcutaneously, intravenously, or intramuscularly. It has the advantage for intravenous injection that the material is distributed throughout the body immediately in the acutely sick individual with practically no risk whatever even of mild reactions. Reactions do sometimes occur, but so far in our experience they have never been of a sort sufficiently disturbing to the attending physician to require any specific means of overcoming them.

Human serum, not being foreign, does not sensitize an individual to any subsequent injection of any other serum, nor does it sensitize the individual to subsequent injections of human serum.

In the experience of many groups of workers convalescent scarlet fever serum has three fields of usefulness: One, the prevention of scarlet fever by passive immunization. Another is in the treatment of the already developed disease. The third is in the treatment of various types of severe hemolytic streptococcal infections not of scarlet fever origin. Only the first two of these properly deserve discussion here.

What can be accomplished in the passive immunization of children who have been exposed intimately, as in the home, to others who have scarlet fever?

In a report of over 800 cases made with Hoyne and S. O. Levinson, of Chicago, it was found that 97 per cent of the children injected did not develop scarlet fever. Of the 3 per cent who were not completely protected, 2 per cent developed a partial picture of modified scarlet fever and only 1 per cent developed the complete disease.

Dr. Wm. H. Park believes that about 15 per cent of the children exposed in the home to others with scarlet fever will develop this disease.

Under these conditions, one can feel that one out of six children who could reasonably be expected to develop scarlet fever will not do so. In other words,

97 per cent did not develop the disease and about 85 per cent of those whom one would expect to develop the disease did not develop it.

It is true that many of these children in this study were in the somewhat better class homes. In homes where the hygienic conditions are not so good, one can expect more exposure and whether this protection would exist in these homes of the lower economic group is not known. That study still has to be made.

What do we feel can be accomplished in the treatment of scarlet fever that has already developed? As with all other acute infectious diseases, the experience has been that, to obtain optimum results, a sufficient amount of the specific serum must be given early in the disease and that the results are definitely, in fact, considered better if the material is administered intravenously rather than intramuscularly or through some other route.

In a large group of cases it has been found that, if the proper dose of serum is given intravenously within thirty-six or forty-eight hours after inception of the disease, not infrequently one secures a dramatic fall of four or five degrees in temperature, a rapid clearing of the rash and of the toxic symptoms, in fact, really abortion of the disease, with the changing of a sick child into a convalescent child, with a rather uninterrupted convalescence.

We found also under these conditions, even if the individuals were severely ill, that the percentage of complications which developed in the severely ill, serum-treated children was about one-half of those which developed in children who were only mildly or moderately ill and who received similar types of general treatment but no specific therapy.

Has the serum any beneficial effect if administered to patients with scarlet fever after the first acute state of illness? In patients who are not brought to the hospital soon enough or who for other reasons are not seen by physicians soon enough to receive any type of specific therapy early in the disease, the results seem to indicate definitely that although such dramatic results as just described do not usually obtain, nevertheless, a very definite and considerable benefit is conferred and, as a matter of fact, apparently some lives have been saved which it was thought would have been lost otherwise.

Even when secondary streptococcal infections have developed, such as adenitis, sinusitis, or a generalized streptococcic peritonitis, many patients have shown marked improvement coincidentally with the use of serum and have gone on to recovery.

QUESTION.—Does scarlatina form a rash following burns?

DR. STIMSON.—I can illustrate that with a case. A nurse came to Willard Parker Hospital who had been operated on in another hospital for a lump on her breast. Two days later she became ill, with a fever of 104° F. and vomited. She developed a rash and was sent to us. She had no sore throat at any time. A dressing of the operative wound in the breast was done on admission and showed an active infection. A pure culture of scarlatinal streptococcus was obtained from the breast wound. Her portal of entry was the operative wound and not the throat.

Scarlet fever rashes in children who have been burned are due to a scarlatinal infection of the burn areas and usually not to throat infections, although the patients may have a typical scarlet fever with the throat as a portal of entry.

QUESTION.—How often does scarlet fever cause sore throat only, with no rash on palate or skin or later development of papilla of the tongue in young children of about the four-year group?

DR. STIMSON.—There is no way of telling except by culturing the organism.

QUESTION.—If the allergic theory is correct, why does not the Dick test become immediately negative following Dick toxin injection?

DR. COOKE.—The Dick test does become negative. If a child with a positive Dick test is given an injection of 500 skin test doses in the morning, and later in the afternoon a thousand skin test doses, the next day the Dick test becomes negative. It does not stay negative more than twenty-four hours or so, but one has desensitized the skin temporarily to small doses of the toxin.

QUESTION.—If a negative Dick test signifies immunity, how can the negative test be explained in acute scarlet fever in the presence of rash and fever?

DR. COOKE.—One does not ordinarily have a negative Dick test in the acute stage of scarlet fever. If one puts toxin into the skin in the acute stage of the scarlet fever, he gets an intensification of rash at that particular area.

QUESTION.—Please give the relative therapeutic merits of convalescent serum and antitoxin.

DR. THALHIMER.—My efforts have been confined to the field of convalescent serum, and I have not had a wide experience with the use of antitoxin. I think those who have should describe their results with the antitoxin. I can only say that in three different cities I know of where convalescent scarlet fever serum has been widely available, more and more men have been using convalescent serum and using less and less of the antitoxin.

QUESTION.—How would you determine the proper dose of serum?

DR. THALHIMER.—In so far as we are concerned, that is determined by actual experience, and we have found that in general a severely sick child up to the age of 5 years should receive 20 c.c. of convalescent serum intravenously. Children from 5 to 10 years, 40 c.c. Children from 10 to 15 years, 60 c.c., and adolescents or adults, 90 to 100 c.c.

QUESTION.—Would it be preferable to give convalescent serum in conjunction with scarlet fever antitoxin?

DR. THALHIMER.—I should say definitely no. It seems the results in the use of either of these indicate that you should use either one or the other, and there is no benefit I know of derived from using both together.

QUESTION.—Have you found that children protected with convalescent serum have given rise to cases among their contacts?

DR. THALHIMER.—It has not been our observation. It may be because we have not had the facilities for making the observation, but I could very well believe that could happen. A child who is resistant to the development of scarlet fever himself could nevertheless harbor streptococci which could convey scarlet fever to some other child.

QUESTION.— Do all cases of scarlet fever have a definite peeling of the skin?

DR. RHOADS.—We should not use the term "all" and "every" in talking about any phase of the practice of medicine. In my experience in practically every case of scarlet fever, peeling has been present, sometimes peeling only very little and found on the edges of the toes and fingers, but in practically every case it is present. There is less if convalescent fever serum or scarlet fever antitoxin is given promptly.

QUESTION.—Why is a Dick test harder to read than a Schick test? Will you describe a positive Dick test?

DR. RHOADS.—I do not agree that a positive Dick test is harder to read than a positive Schick test. The test should be read from twenty to twenty-four hours after it is made, only in that interval. Any area of erythema from pale pink to bright pink more than 0.5 cm. in diameter should be regarded as a positive Dick test. There is no induration at the site of injection of the toxin as there is in the Schick test.

QUESTION.—Does commercial Dick test material represent more than one strain of streptococcus toxin?

DR. RHOADS.—Yes.

QUESTION.—Should a Dick test always be controlled with heated toxin?

DR. RHOADS.—No, if an original Dick test is controlled by heated toxin, many positive Dick tests will be interpreted as pseudoreactions. The control with heated toxin should be used only in those persons found to be positive on retest. If persons are found to be positive on retest and another dose of toxin finds them two weeks later in the same situation, then it is advisable to use a control of heated toxin, but only under those conditions.

QUESTION.—At what age is active immunization advisable? As a public health measure should patients with strongly suspected scarlatinal symptoms be quarantined?

DR. RHOADS.—In answer to the first question, we have immunized patients from a year and one-half on. It is our experience that children immunized that early do not retain their immunity as well as children immunized a year or two later. As a matter of practical experience, we usually advise immunization at the preschool age if it can be done at that time. Of course, it can be done at any age from three to five. In a scarlet fever outbreak persons strongly suspected of having scarlet fever should be quarantined until the diagnosis is certain.

QUESTION.—Would you immunize, as a routine procedure, even in spite of the mild character of the scarlet fever?

DR. RHOADS.—By all means. We know one of the characteristics of scarlet fever is the severe complications which may follow mild attacks, and one never knows when a given case of scarlet fever will be a severe one. I should say by all means the answer is yes.

QUESTION.—How do you explain the absence of a positive Dick test in the newborn?

DR. RHOADS.—I do not explain it because I know a positive Dick test occurs sometimes. If the mother is Dick-positive, the newborn infant is likely to be Dick-positive. If the mother is Dick-negative, the newborn child is likely to be Dick-negative. We explain that by the factor of inherited immunity. That immunity is lost, of course, from the sixth to the eighth month usually.

There is one thing I would like to say in regard to Dr. Cooke's statement. He says the Dick test is positive always in the acute phase of scarlet fever. I published a report two or three years ago in the *American Journal of Diseases of Children* with Dr. Gasul, in which we found the Dick test may become negative at the end of twenty-four hours, a higher percentage are negative at the end of forty-eight hours after the onset of the rash, and most are negative by the end of a week after the start of scarlet fever. Our results would not coincide with that statement.

DR. VELDEE.—I have three questions here all of which are alike—in other words, asking where and when this material may be obtained, which has served as the basis for my report in this panel discussion. Obviously it is still in the research stage and the basic toxin from which it is made probably is controlled by the patent held by the Scarlet Fever Committee. It will remain for future research work to establish fully whether the method I am using is superior to the present one, and if it proves to be, it will be up to the Scarlet Fever Committee to release it if they see fit.

There are five other questions all bearing on the use of the new chemotherapy, namely sulphanilamide, in the prevention or treatment of scarlet fever. I think you all appreciate that the use of this drug is still somewhat experimental. We have not, as far as I know, any positive evidence of its value, at least over any large series of cases, in the treatment of scarlet fever. My own personal opinion is that, if the drug is as good as suggested by limited trial, it will afford a very excellent way of preventing the septic complications.

Scarlet fever antixonin merely neutralizes the erythrogenic toxin but, if given early, also will prevent septic complications. However, it has no value in preventing septic complications already present and herein may lie the value of sulphanilamide treatment. I would like to see some one who has access to a large group of scarlet fever cases try it out. The trial should involve a large group of cases and it should also include a satisfactory control group. Another question is: Have you seen Dr. Robinson's report of intradermal scarlet fever immunization in the *Journal of Immunology* last November? His report was based on twenty-nine cases, and if any of you have done research work in scarlet fever you know how misleading a study involving only twenty-nine cases may be. For example I had good results on ninety institutional children with one dose of toxoid. I tried the same dose on a large group of grammar school children, and the results proved very disappointing. Nevertheless, I believe that Dr. Robinson's observation is correct and can be duplicated in a much larger group.

I have received two questions regarding the appropriate age for immunization. It has been touched upon by Dr. Rhoads. I would like to add that until we get a method of active immunization which is accepted by the physicians generally and public health authorities as well, we do not need to worry so much as to when we will immunize. We are still concerned with the problem of a suitable antigen.

Another question about the strain used in preparing the toxin. I would like to add one more point to what Dr. Rhoads said in answering a similar question. In making the antitoxin, there is a fifth strain added because it appears to stimulate the horse to greater antitoxin production.

Another point along this same line might also be emphasized. Some ten years ago, the manufacturers were having great difficulty in meeting the minimum requirements of 200 units of scarlet fever antitoxin per cubic centimeter. At the present time the manufacturers are turning out serum containing as high as 5,000 or 6,000 units per cubic centimeter. Therefore you have in your hands a much better therapeutic agent than you had a few years ago.

DR. STIMSON.—I have a question here which I tried to answer before but at first could not read it: A baby, two years old, with a septic type of throat, with otitis media, cervical adenitis, acutely ill for five weeks, no rash at any time, but three successive nurses coming down with typical scarlet fever each after four to seven days after coming on duty.

I think this baby had a scarlet fever infection without rash or the rash may have been so mild as to be overlooked.

QUESTION.—Does hematuria mean toxin circulating in the blood or that the kidney damage has been done by toxin previously circulating but eliminated at the onset of the nephritis?

DR. STIMSON.—There is much difference of opinion as to the cause of nephritis in scarlet fever, some maintaining it is of bacterial and some of toxic origin. In any case, the common type of nephritis is glomerular with hematuria.

DR. COOKE.—The question regarding the loss of skin sensitivity early in scarlet fever and the presence of a negative Dick test early in scarlet fever which Dr. Rhoads mentioned should be commented on.

Sensitivity to small amounts of toxin, such as one skin dose, may be lost early in scarlet fever from partial early sensitization, but, if one uses a somewhat larger amount of toxin, say 10 or 15 skin doses, or 25, this will produce an intensification of rash at this area.

I want to take this opportunity, however, to discuss one point raised by Dr. Rhoads, viz., that nurses who had been immunized against the toxin of scarlet fever showed fewer sore throats the next year, as being evidence of immunization against the scarlatinal infection. I am afraid Dr. Rhoads is falling into a common error in assuming that streptococcic infections exist every year to the same degree. Certainly we should have to carry out observations over a considerable period of years, because it is well known that throat infections and streptococcic infections are far more common in certain years than in others. Because nurses had been "immunized" and showed fewer infections the next year would be no proof the immunization was responsible for this decrease in the infection.

MEETING OF REGION III OF THE AMERICAN ACADEMY OF PEDIATRICS

At the meeting of Region III, Oct. 14-16, 1937, in Chicago, an extensive scientific program was given on Thursday morning, October 14, by members of the staff of Presbyterian Hospital, on Thursday afternoon by the staff of Cook County Children's Hospital, on Friday morning by the staff by Bobs Roberts Memorial Hospital, and on Friday afternoon by members of the staff of the Sarah Morris and Mercy Hospitals. The final scientific session on Saturday morning was given at the Children's Memorial Hospital by members of the staff. Many of the presentations were interesting case reports, and there were a large number of original communications on important subjects. Luncheon on the three days was served at the Cook County Nurses' Home, the University of Chicago, and at the Children's Memorial Hospital. On Thursday evening a reception was held by the Chicago Pediatric Society at the Lake Shore Athletic Club where dinner was served.

The following is a report of the meeting of the state chairmen of Region III held at the Lake Shore Athletic Club on Oct. 14, 1937.

Dr. A. Graeme Mitchell, regional chairman, presided. The following were present: Dr. Franklin P. Gengenbach, Colorado; Dr. Maurice L. Blatt, Illinois; Dr. Matthew Winters, Indiana; Dr. Edgar E. Martmer, Michigan; Dr. E. J. Huenekens, Minnesota; Dr. Park J. White, cochairman from Missouri; Dr. Ralph E. Pray, North Dakota; Dr. Sterling H. Ashmun, Ohio; Dr. Goldie E. Zimmerman, South Dakota; Dr. Abraham B. Schwartz, Wisconsin; and Dr. E. G. Padfield, Kansas. Dr. E. W. Hancock represented Dr. Clyde Moore, Nebraska, who was unable to attend. Dr. Frederick B. Miner, Flint, Mich., was present by invitation.

Several chairmen submitted reports from their states, and others promised to send their reports in writing.

The following are names of applicants who were recommended to membership by the regional committee to the Executive Board:

Dr. Ernest Ekermeyer, Xenia, Ohio.
Dr. Faith Hardy, Grand Rapids, Mich.
Dr. Clair L. Douglas, Detroit, Mich.

The following are names of applicants who were recommended for election when and if they secured the certification of the American Board of Examiners in Pediatrics:

Dr. Clara D. Tigay, Chicago, Ill.
Dr. Raymond W. Frankman, Massillon, Ohio
Dr. Harold O. Lund, Middletown, Ohio
Dr. Dwight A. Weir, Mansfield, Ohio
Dr. John W. Maroney, Detroit, Mich.
Dr. James J. Donahue, East St. Louis, Ill.
Dr. Thomas P. Saltiel, Chicago, Ill.
Dr. Mark F. Osterlin, Traverse City, Mich.
Dr. Oliver E. Ehrhardt, Springfield, Ill.
Dr. William Bryant Richards, St. Cloud, Minn.

There was discussion of the fact that the chairman of each state should first pass upon all applicants from his state before they were considered by the regional committee. The regional chairman explained that this was the procedure followed, although in a few instances of applications received by him before he became regional chairman this was not the case.

There was discussion of the matter of applicants who did not confine their practice to pediatrics. It was moved by Dr. Martmer and seconded by Dr. Pray that it be the plan of the regional committee not to recommend to the executive board any applicant who did not limit his practice to pediatrics unless he was engaged in the type of work which by specific circumstances showed that he contributed directly to the benefit of pediatrics. It seemed to be the sense of the meeting that requirements should be strictly adhered to.

After motion by Dr. Martmer it was recommended that the regional committee suggest to the Executive Board that the Academy make some special study, probably by a committee, regarding the thymus gland. This might perhaps take the form of a round table discussion at one of the Academy meetings. Dr. Martmer explained that members from Michigan felt that, if it were possible to make some definite statement, even if it were negative, regarding the symptoms produced by the thymus, it would be helpful.

Dr. Martmer invited Region III to meet in Detroit in 1938. This invitation was accepted with alacrity and gusto. The time of the meeting was to be decided by the Michigan group.

Dr. White suggested that if Dr. Berger was unable to continue as cochairman from Missouri because of his health, Dr. Walthall would be an acceptable chairman. Information received by the regional chairman indicates that Dr. Berger wishes to retain his cochairmanship at the present. He is said to be in good physical condition and would be glad to cooperate in every way.

Dr. Martmer recommended for associate membership, Dr. Franklin Top, Detroit. The regional chairman will request Dr. Martmer to write directly to the executive committee in making this recommendation.

There was discussion of recommendations for associate regional chairman. The regional chairman stated that he would get the opinion of each state chairman by letter; it was moved that he then make these recommendations, after consideration, to the executive committee.

Dr. Krafft, Chicago, was allowed the floor. He wished to call the attention of the regional committee and of the Academy to the underprivileged (precriminal) child. He thought that contacts should be made with educational organizations and with lay societies and organizations; that the physician as well as the laity should be educated; that all children should be examined annually and that efforts should be made to secure legislation concerning these subnormal persons.

It was the opinion of the meeting that many of these contacts were already being made in the different states and that no particular recommendation need be made by the regional committee to the Executive Board.

Academy News

Registration for the Eighth Annual Meeting of the American Academy of Pediatrics at the Hotel Del Monte, Del Monte, Calif., June 9-11, begins at 9:00 A.M. Thursday, June 9. Scientific papers and panel discussions will be heard Thursday and Friday mornings. The general meeting, which concludes with the installation of the new president, will be Saturday morning. The afternoon of each day, from 2 o'clock on, will be devoted to the round table discussions, twelve in all, each to be given twice.

The **New Jersey Section of the Academy of Pediatrics** met at the Academy of Medicine in Newark, Dec. 8, 1937.

In the afternoon Dr. William Wolf gave an extensive discussion of recent advances in pediatric endocrinology. This was followed by a panel discussion, "Diarrheal Diseases of Infancy," with the discussion centering on epidemic diarrhea of the newborn. Dr. F. Elmer Johnson led the panel, assisted by Dr. William Astapol, Dr. Harold Abramson, Dr. Joseph Felsen, and Dr. Samuel Karelitz.

In the evening the dinner was enthusiastically attended by about thirty-five members. Following the dinner there was a round table discussion, "How We Can Improve the Practice of Pediatrics." Dr. S. H. Nichols announced appointments of the members to a comprehensive list of committees covering all phases of infant care and child hygiene. Then he called on each member in rotation to give his own specific ideas on how best to improve the character and amount of pediatric practice in his community. Dr. LeRoy A. Wilkes summarized these suggestions as follows:

1. We must constantly improve our professional equipment and translate our scientific training into service so that our patients will feel they are getting the service they came for.
2. We must have a definite program as pediatrists so that we can advise and help the various organizations and groups that are interested in child health.
3. We as pediatrists should familiarize ourselves with the problems of adolescence.
4. We must each have a definite program and a business-like schedule so as to give the most service in the time at our disposal.

F. W. LATHROP.

News and Notes

The seventh annual meeting of the **Tennessee State Pediatric Society** was held on Tuesday, April 12, 1938, at Nashville, Tenn. Dr. Eugene Rosamond, Memphis, is president. Dr. Kinsey M. Buck, Memphis, is secretary-treasurer. The Tennessee State Pediatric Society is a section of the Tennessee State Medical Society.

Erratum

In the article, "Critical Review of Congenital Syphilis, Part I," by Dorothy V. Whipple, M.D., and Ethel C. Dunham, M.D., which appeared in the March issue of the Journal, the references to Ingraham should be numbered 22 instead of 23 as they now appear, on pages 390-393.